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FOR: SUBSTITUTED METHYLENE AMIDE DERIVATIVES AS MODULATORS OF PROTEIN TYROSINE PHOSPHATASES (PTPS)

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Commissioner for Patents
Alexandria, Virginia 22313

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02100078.1

PRIORITY DOCUMENT
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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Substituted methylene amide derivatives as modulators of protein tyrosine phosphatases (PTPs)

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Substituted methylene amide derivatives as Modulators of Protein Tyrosine Phosphatases (PTPs)

Field of the invention

The present invention is related to substituted methylene amide derivatives of formula (I), in particular for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS). The compounds of this invention are particularly useful in the treatment of type II or I diabetes. Specifically, the present invention is related to substituted methylene amide derivatives for the modulation, notably the inhibition of the activity of PTPs, in particular of PTP1B.

Background of the invention

The prevalence of insulin resistance in glucose intolerant subjects is well known. Reaven et al (*American Journal of Medicine*, 60, 80 (1976)) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance exists in a diverse group of non-obese, non-ketotic subjects. These subjects ranged from borderline glucose tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (IDDM) and non-insulin dependent (NIDDM) subjects.

Coincident with sustained insulin resistance is the more easily determined hyperinsulinemia, which may be measured by accurate determination of circulating plasma insulin concentration in the plasma of subjects. Hyperinsulinemia may be present as a result of insulin resistance, such as is in obese and/or diabetic (NIDDM) subjects and/or glucose intolerant subjects, or in IDDM subjects, as a consequence of over injection of insulin compared with normal physiological release of the hormone by the endocrine pancreas.

The association of hyperinsulinemia and insulin resistance with obesity and with ischemic diseases of the large blood vessels (e.g. atherosclerosis) has been well established by numerous experimental, clinical and epidemiological studies (Stout, *Metabolism*, 34, 7 (1985)). Statistically significant plasma insulin elevations at 1 and 2 hours after oral glucose load correlate with an increased risk of coronary heart disease.

Since most of these studies actually excluded diabetic subjects, data relating the risk of atherosclerotic diseases to the diabetic condition are not as numerous, but point in the same direction as for non-diabetic subjects. However, the incidence of atherosclerotic diseases in morbidity and mortality statistics in the diabetic population exceeds that of the nondiabetic population (Pyorala et al; Jarrett *Diabetes/Metabolism Reviews*, 5, 547 (1989)).

The association of hyperinsulinemia and insulin resistance with Polycystic Ovary Syndrome (PCOS) is also well acknowledged (Diamanti-Kandarakis et al.; Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome; *European Joumal of Endocrinology* 138, 269-274 (1998), Andrea Dunaif; Insulin Resistance and the Polycystic Ovary Syndrome : Mechanism and Implications for Pathogenesis; *Endocrine Reviews* 18(6), 774-800 (1997)).

The independent risk factors obesity and hypertension for atherosclerotic diseases are also associated with insulin resistance. Using a combination of insulin/glucose clamps, tracer glucose infusion and indirect calorimetry, it was demonstrated that the insulin resistance of essential hypertension is located in peripheral tissues (principally muscle) and correlates directly with the severity of hypertension (DeFronzo and Ferrannini, *Diabetes Care*, 14, 173 (1991)). In hypertension of obese people, insulin resistance generates hyperinsulinemia, which is recruited as a mechanism to limit further weight gain via thermogenesis, but insulin also increases renal sodium re-absorption and stimulates the sympathetic nervous system in kidneys, heart, and vasculature, creating hypertension.

It is assumed that insulin resistance is usually the result of a defect in the insulin receptor signaling system, at a site post binding of insulin to the receptor. Accumulated scientific evidence demonstrating insulin resistance in the major tissues which respond to insulin (muscle, liver, adipose), strongly suggests that a defect in insulin signal transduction resides at an early step in this cascade, specifically at the insulin receptor kinase activity, which appears to be diminished (Mounib Elchebly, Alan Cheng, Michel L. Tremblay; Modulation of insulin signaling by protein tyrosine phosphatases; *J. Mol. Med.* 78, 473-482 (2000)).

Protein-tyrosine phosphatases (PTPs) play an important role in the regulation of phosphorylation of proteins and represent the counterparts of kinases. Among classical PTPs, there are two types : (i) non-receptor or intracellular PTPs and (ii) receptor-like PTPs. Most intracellular PTPs contain one catalytic domain only, whereas most receptor-like enzymes contain two. The catalytic domain consists of about 250 amino acids (Niels Peter Hundahl Moller et al. Protein tyrosine phosphatases (PTPs) as drug targets: Inhibitors of PTP-1B for the treatment of diabetes; *Current Opinion in Drug Discovery & Development* 3(5), 527-540 (2000)).

The interaction of insulin with its receptor leads to phosphorylation of certain tyrosine molecules within the receptor protein, thus activating the receptor kinase. PTPs dephosphorylate the activated insulin receptor, attenuating the tyrosine kinase activity. PTPs can also modulate post-receptor signaling by catalyzing the dephosphorylation of cellular substrates of the insulin receptor kinase. The enzymes that appear most likely to closely associate with the insulin receptor and therefore, most likely to regulate the insulin receptor kinase activity, include PTP1B, LAR, PTP-alpha and SH-PTP2 (Lori Klaman et *al.*; Increased Energy Expenditure, Decreased Adiposity, and Tissue-specific insulin sensitivity in Protein-Tyrosine Phosphatase 1B-Deficient Mice; *Molecular and Cellular Biology*, 5479-5489 (2000)).

PTP1B is a member of the PTP family. This 50 kDa protein contains a conserved phosphatase domain at residues 30-278 and is localized to the cytoplasmic face of the

endoplasmic reticulum by its C-terminal 35 residues. Its interactions with other proteins are mediated by proline-rich regions and SH2 compatible sequence. PTP1B is believed to act as a negative regulator in insulin signaling.

McGuire et al. (*Diabetes*, 40, 939 (1991)) demonstrated that non-diabetic glucose intolerant subjects possessed significantly elevated levels of PTP activity in muscle tissue vs. normal subjects, and that insulin infusion failed to suppress PTP activity as it did in insulin sensitive subjects.

Meyerovitch et al. (*J. Clinical Invest.*, 84, 976 (1989)) observed significantly increased PTP activity in the livers of two rodent models of IDDM, the genetically diabetic BB rat, and the STZ-induced diabetic rat. Sredy et al. (*Metabolism*, 44, 1074, (1995)) observed similar increased PTP activity in the livers of obese, diabetic ob/ob mice, which represent a typical rodent model of NIDDM.

Zhang et *al* (*Curr. Opin. Chem. Biol.*, 5(4), 416-23 (2001)) found that PTPs are also implicated in a wide variety of other disorders, including cancer. Bjorge, J.D. et *al.* (*J. Biol. Chem.*, 275(52), 41439-46 (2000)) indicates that PTP1B is the primary protein-tyrosine phosphatase capable of dephosphorylating c-Src in several human breast cancer cell lines and suggests a regulatory role for PTP1B in the control of c-Src kinase activity.

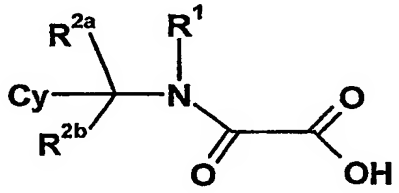
Pathre et al (*J. Neurosci. Res.*, 63(2), 143-150 (2001)) describes that PTP1B regulates neurite extension mediated by cell-cell and cell-matrix adhesion molecules. Further, Shock L. P et al. (*Mol. Brain. Res.*, 28(1), 110-16 (1995)) demonstrates that a distinct overlapping set of PTPs is expressed in the developing brain and retinal Mueller glia, including 2 novel PTPs that may participate in neural cell communication.

The insulin receptor (IR) is a prototypical tyrosine kinase receptor whose ligand binding and dimerization results in auto-phosphorylation on multiple tyrosines. This is followed by the recruitment and phosphorylation of IRS1-4 (depending on the tissue) and PI3K. Although vanadium-containing compounds have been known since the 19th century to

alleviate diabetes, it was understood only recently that these inhibitors stimulate the insulin signaling pathway by blocking PTP action. Evidence for the involvement of the IR (insulin receptor) and IRS-1 in this phenotype was that both proteins show increased tyrosine phosphorylation in the PTP1B-mutated mice. The available data strongly suggest that in particular PTP1B is a promising target for the development of drugs to treat diabetes and obesity (Brian P. Kennedy and Chidambaram Ramachandran; Protein Tyrosine Phosphatase-lB in Diabetes; *Biochemical Pharmacology*, Vol. 60, 877-883, (2000)).

Summary of the invention

The present invention relates to substituted methylene amide derivatives of formula (I).



(I)

Such compounds are suitable for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS). The compounds of this invention are inhibitors of PTPs.

Detailed description of the invention

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"PTPs" are protein tyrosine phosphatases and include for instance PTP1B, TC-PTP, PTP-β, DEP-1, LAR, SHP-1, SHP-2, GLEPP-1, PTP-κ, PTP-μ, VHR, hVH5, LMW-PTP, PTEN.

~~"C_1-C_{12}-alkyl" refers to straight or branched monovalent alkyl groups having 1 to 12~~ carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl, n-octyl, n-nonyl and the like in straight or branched forms thereof.

"Aryl" refers to an unsaturated, aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"C_1-C_{12}-alkyl aryl" refers to C_1-C_{12}-alkyl groups having an aryl substituent, including benzyl, phenethyl and the like.

"Heteroaryl" refers to a monocyclic heteromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl; 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl,

pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"C_1-C_{12}-alkyl heteroaryl" refers to C_1-C_{12}-alkyl groups having a heteroaryl substituent, including 2-furylmethyl, 2-thienylmethyl, 2-(1H-indol-3-yl)ethyl and the like.

"Alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-$CH{=}CH_2$), n-2-propenyl (allyl, -$CH_2CH{=}CH_2$) and the like.

"Alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-$C{\equiv}CH$), propargyl (-$CH_2C{\equiv}CH$), and the like.

"Acyl" refers to the group –C(O)R where R includes "C_1-C_{12}-alkyl", "aryl", "heteroaryl", "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Acyloxy" refers to the group –OC(O)R where R includes "C_1-C_{12}-alkyl", "aryl", "heteroaryl", "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Alkoxy" refers to the group –O-R where R includes "C_1-C_{12}-alkyl" or "aryl" or "heteroaryl" or "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes "C_1-C_{12}-alkyl" or "aryl" or "heteroaryl" or "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen or C_1-C_{12}-alkyl or aryl or heteroaryl or "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Acylamino" refers to the group –NR(CO)R' where each R, R' is independently hydrogen or "C_1-C_{12}-alkyl" or "aryl" or "heteroaryl" or "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyl" refers to group "–SO_2-R" wherein R is selected from H, "aryl", "heteroaryl", "C_1-C_{12}-alkyl", "C_1-C_{12}-alkyl" substituted with halogens e.g. an –SO_2-CF_3 group, "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Sulfoxy" refers to a group "–S(O)-R" wherein R is selected from H, "C_1-C_{12}-alkyl", "C_1-C_{12}-alkyl" substituted with halogens e.g. an –SO-CF_3 group, "aryl", "heteroaryl", "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl".

"Thioalkoxy" refers to groups –S-R where R includes "C_1-C_{12}-alkyl" or "aryl" or "heteroaryl" or "C_1-C_{12}-alkyl aryl" or "C_1-C_{12}-alkyl heteroaryl". Preferred thioalkoxy groups include thiomethoxy, thioethoxy, and the like.

The above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and "heteroaryl" etc. groups may optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C_1-C_{12}-alkyl", "C_1-C_{12}-alkyl aryl", "C_1-C_{12}-alkyl heteroaryl", "C_2-C_{12}-alkenyl", "C_2-C_{12}-alkynyl", primary, secondary or tertiary amino groups or quarternary ammonium moieties, "acyl", "acyloxy", "acylamino", "aminocarbonyl", "alkoxycarbonyl", "aryl", "heteroaryl", carboxyl, cyano, halogen, hydroxy, mercapto, nitro, sulfoxy, sulfonyl, alkoxy, thioalkoxy, trihalomethyl and the like. Alternatively said substitution could also comprise situations where neighboring substituents have undergone ring closure, notably when viccinal functional substituents are involved, thus forming e.g. lactams, lactons, cyclic anhydrides, but also acetals, thioacetals, aminals formed by ring closure for instance in an effort to obtain a protective group.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes of the below-specified compounds of formula (I). Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), as well as salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and poly-galacturonic acid. Also comprised are salts which are formed from organic or inorganic bases selected in the group consisting of alkali metals (sodium, potassium or lithium), alkaline earth metals (e.g. calcium or magnesium), ammonium, primary, secondary or tertiary alkyl amines (e.g. morpholine, Me-D-glucamine, tromethamine, diethanolamine or ethylenediamine), as well as amines of formula –NR,R',R" wherein R, R', R" is independently hydrogen, alkyl or benzyl.

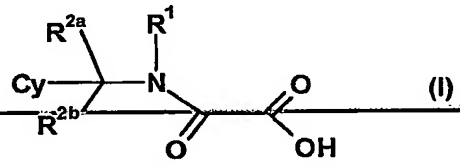
"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the activity disclosed herein. The term "indirectly" also encompasses prodrugs which may be converted to the active form of the drug via endogenous enzymes or metabolism. Said prodrug is comprised of the active drug compound itself and a chemical masking group that temporarily suppresses activity.

"Enantiomeric excess" (ee) refers to the products that are obtained by an asymmetric synthesis, i.e. a synthesis involving non-racemic starting materials and/or reagents or a synthesis comprising at least one enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded. In the absence of an asymmetric synthesis, e.g. the corresponding esters of the substituted methylene amides of formula I, racemic products are usually obtained that do however also have a PTP inhibiting activity.

Said formula also comprises its tautomers, its geometrical isomers, its optically active forms as enantiomers, diastereoisomers and its racemate forms, as well as pharmaceutically

acceptable salts thereof. Preferred pharmaceutically acceptable salts of the formula (I), are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen sulfate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, *para*-toluenesulfonate salts and N-methyl-D-glucamine sodium salts.

The substituted methylene amide derivatives according to the present invention are those of formula (I):



(I)

Formula (I) comprises also the geometrical isomers, the optically active forms, including enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof.

The substituents R^1, R^{2a}, R^{2b} and Cy within Formula (I) are defined as follows :

R^1 is selected from the group consisting of substituted or unsubstituted (C_1-C_{12})-alkyl, preferably substituted or unsubstituted (C_1-C_6)-alkyl, substituted or unsubstituted (C_2-C_{12})-alkenyl, substituted or unsubstituted (C_2-C_{12})-alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted (3-8-membered) cycloalkyl or heterocycloalkyl, substituted or unsubstituted (C_1-C_{12})-alkyl-aryl or substituted or unsubstituted (C_1-C_{12})-alkyl-heteroaryl, substituted or unsubstituted (C_2-C_{12})-alkenyl-aryl or -heteroaryl, substituted or unsubstituted (C_2-C_{12})-alkynyl-aryl or -heteroaryl.

In a preferred embodiment of the present invention, R^1 is A wherein A is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted

3-8 membered heterocycloalkyl or 3-8 membered cycloalkyl, in particular a substituted or unsubstituted phenyl.

In another preferred embodiment, A is a moiety of the formula $-CH_2$-A or $-CH_2-CH_2$-A, with A being a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted 3-8-membered heterocycloalkyl or a substituted or unsubstituted 3-8-membered cycloalkyl. In particular, A may be a phenyl, pyridinyl, benzo-1,3-dioxolenyl, biphenyl, naphtyl, quinoxalinyl, thiazolyl, thienyl, furanyl or a piperidinyl group, being optionally substituted by 1 or 2 moieties selected from the group consisting of cyano, halogen, NO_2, (C_1-C_6)alkoxy, aryloxy or heteroaryloxy, (C_1- C_6)thioalkoxy, optionally halogenated (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl, (C_1-C_6)alkyl aryl or heteroaryl, (C_2-C_6)alkenyl aryl or heteroaryl, (C_2-C_6)alkynyl aryl or heteroaryl, $-COR^3$, $-COOR^3$, $-CO-NR^3R^{3'}$, $-NHCOR^3$, $-COR^3$, $-CO-Y-R^3$ wherein R^3 is (C_1-C_6)alkyl or (C_2-C_6)alkenyl, $-SOR^3$, $-SO_2R^3$, $-SO_2NR^3R^{3'}$ with R^3, $R^{3'}$ being independently from each other selected from the group consisting of H, straight or branched (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2- C_6)alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl.

R^{2a} and R^{2b} are each independently from each other selected from the group comprising or consisting of H or substituted or unsubstituted (C_1-C_{12})alkyl, preferably R^{2a} and R^{2b} are each H.

Cy is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted 3-8-membered cycloalkyl or heterocycloalkyl.

Such aryl or heteroaryl include phenyl, naphthyl, phenantrenyl, pyrrolyl, furyl, thienyl, imidazolyl, pyridyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, benzo(1,2,5)oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, tetrazolyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzopyrimidinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl,

isobenzothienyl, indolyl, isoindolyl, 3*H*-indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, pyridazinyl, pyrimidyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, xanthenyl, benzoquinolyl, oxolanyl, pyrolidinyl, pyrazolidinyl, 2H-benzo[d]1,3-dioxolenyl, indanyl, imidazolidinyl, 1,2,4-oxadiazolidinyl, 1,2,5-oxadiazolidinyl, 1,3,4-oxadiazolidinyl or isoxazolidinyl.

In particular, Cy is a substituted or unsubstituted thienyl or phenyl, e.g. a biphenyl group.

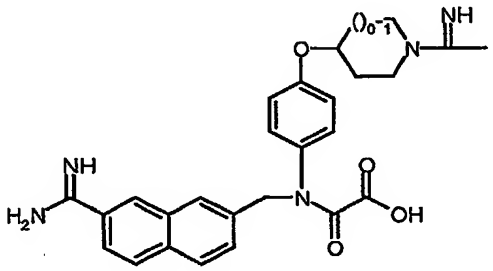
More specifically, Cy is a thienyl, phenyl which may be substituted by an aryl or heteroaryl, e.g. an oxadiazole, or a cycloalkyl moiety, or Cy is thienyl, phenyl which may be substituted by 1 or 2 moieties selected from the group consisting of NH-CO-R^3, -SO_2-$NR^3R^{3'}$ or –CO-$NR^3R^{3'}$ in which R^3, $R^{3'}$ are independently selected from H, (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl, (C_1-C_{12})alkyl aryl or heteroaryl, (C_2-C_{12})alkenyl-aryl or -heteroaryl, (C_2-C_{12})alkynyl-aryl or -heteroaryl.

Particularly preferred is where $R^{3'}$ is H and R^3 is selected from the group consisting of diphenyl-ethyl, dodecyl, octyl, 4-pentyl-benzyl, 4-phenoxy-phenethyl, ethyl-thiophen-2-yl, pentadecyl, tridecyl, hexyloxy-phenyl, (2-ethyl)-hexyl.

Particularly preferred compounds of the invention are those wherein R^{2a} and R^{2b} are each H, R^1 is –CH_2-A, or -CH_2–CH_2-A with A being phenyl or thienyl, optionally substituted by cyano, halogen, methoxy, hydroxy, phenoxy, -NO_2, trifluoromethyl while Cy is a thienyl, phenyl or biphenyl being substituted by -SO_2R^3, –CO-$NR^3R^{3'}$ in which $R^{3'}$ is H and R^3 is (C_6-C_{12})alkyl.

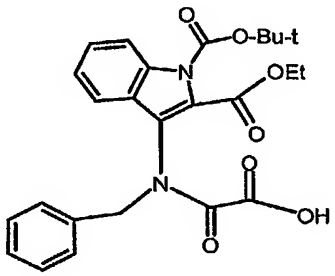
Some very few compounds falling into formula (I) are disclosed in the prior art. Said compounds are the following:

a) Compounds of formula (I), wherein Cy is an amidinonaphthyl moiety, R^1 is a phenyl group which is para-substituted by a–O-piperidine or –O-pyrrolidine moiety.



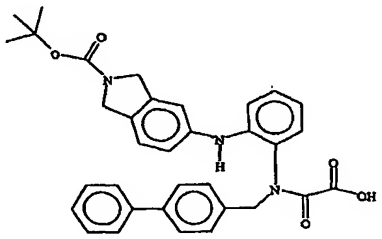
Such compounds are disclosed in WO 96/16940 (Yamanouchi Pharmaceutical Co.) and are said to have an antiplatelet aggregation effect. They purportedly inhibit activated blood coagulation factor X and are useful as an antithrombotic agent.

b) A compound of formula (I), wherein Cy is a phenyl group, R^{2a} and R^{2b} are each H, R^1 is an indole moiety substituted in 1-position with an ethyl carboxylate group and in 2-position with a tert.-butyl carboxylate group.



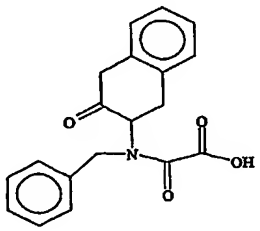
The above single compound is disclosed in EP-483881 (Merrel Dow Pharmaceuticals) and is said to be useful for the treatment of neurodegenerative disease states.

c) A compound of formula (I), wherein Cy is a biphenyl group, R^{2a} and R^{2b} are each H, R^1 is a phenyl group ortho-substituted with a tert-butyl 5-aminoisoindoline-2-carboxylate.



This single compound is mentioned in WO 00/23428 (Takeda Chemical Industries Ldt.) as an intermediate compound in the synthesis of 1,5-benzodiazepine compounds. No medical use has been associated with said compound.

d) A compound of formula (I), wherein Cy is a phenyl group, R^{2a} and R^{2b} are each H, R^1 is a 2,3,4-trihydronaphtalen-1-one.



The above compound is disclosed in *J.Chem.Soc., Perkin Trans* 1(10), p.2126-33 (1980) without any biologic activity or therapeutic application.

Specific compounds of the present invention are in particular those of the group consisting of:

(benzyl{4-[(dodecylamino)carbonyl] benzyl}amino)(oxo)acetic acid

benzyl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid, 2-amino-2-hydroxy-methyl)-1,3-propanediol salt

benzyl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid, 1-deoxy-1-(methylamino)glucitol salt

oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}acetic acid

(benzyl{4-[(pentadecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

(benzyl{4-[(tridecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[benzyl(4-{[dodecyl(methyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

{(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]amino}-(oxo)-acetic acid

([1-(tert-butoxycarbonyl)-4-piperidinyl]{4-[(dodecylamino)carbonyl]benzyl}-amino)(oxo)-acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid, 1-deoxy-1-(methylamino)glucitol salt

{{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid, 1-deoxy-1-(methylamino)glucitol salt

({[1-(tert-butoxycarbonyl)-4-piperidinyl]methyl}{4-[(dodecylamino)carbonyl]-benzyl}-amino)(oxo)acetic acid

oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetic acid

oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetic acid, 1-deoxy-1-(methylamino)glucitol salt

[benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetic acid

oxo{[4-(trifluoromethyl)benzyl][4-(10-undecenoylamino)benzyl]amino}acetic acid

oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)benzyl]amino}acetic acid

oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)benzyl]amino}acetic acid, 1-deoxy-1-(methylamino)glucitol salt

{benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetic acid

{{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)acetic acid

oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]-amino}acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl)benzyl]amino}-(oxo)-acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl)benzyl]amino}-(oxo)-acetic acid, 1-deoxy-1-(methylamino)glucitol salt

[{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-methyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-methyl)amino](oxo)acetic acid, 1-deoxy-1-(methylamino)glucitol salt

[{4-[(dodecylamino)carbonyl]benzyl}(2-carboxy-1-phenylethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-methoxy-1-methylethyl)amino](oxo)acetic acid

(4-bromo{4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

([2-(3-chlorophenyl)ethyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[2-(3-methoxyphenyl)ethyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[(d,l)-trans-2-phenylcyclopropyl]amino}-(oxo)acetic acid

([(d,l)-trans-2-(benzyloxy)cyclopentyl]{4-[(dodecylamino)carbonyl]benzyl}-amino)(oxo)-acetic acid

({4-[(dodecylamino)carbonyl]benzyl}-4-phenoxyanilino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-(oxo)-acetic acid

((1-benzyl-4-piperidinyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[2-(4-phenoxyphenyl)ethyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[2-(2-phenoxyphenyl)ethyl]amino}(oxo)acetic acid

((2-[1,1'-biphenyl]-4-ylethyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

(([1,1'-biphenyl]-3-ylmethyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

(3-(benzyloxy){4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

([4-(benzoylamino)benzyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

N-(carboxycarbonyl)-N-{4-[(dodecylamino)carbonyl]benzyl}-3-phenyl-beta-alanine

{{4-[(dodecylamino)carbonyl]benzyl}[4-(1,2,3-thiadiazol-4-yl)benzyl]amino}-(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-pentylbenzyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(1-phenylethyl)amino](oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino}(oxo)acetic acid

(benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{3-[(dodecylamino)carbonyl]benzyl}[4-(methylsulfonyl)benzyl]amino}(oxo)acetic acid

((3-cyanobenzyl){3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{3-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

[(4-chlorobenzyl)(3-{[(4-pentylbenzyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

oxo{[4-({[2-(2-thienyl)ethyl]amino}carbonyl)benzyl][4-(trifluoromethyl)benzyl]-amino}-acetic acid

{benzyl[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}-(oxo)acetic acid

{(3-cyanobenzyl)[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

{(4-chlorobenzyl)[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

{[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoro-methyl)benzyl]amino}(oxo)acetic acid

((3-cyanobenzyl){[3'-({[2-(4-phenoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}amino)(oxo)acetic acid

oxo{{[3'-({[2-(4-phenoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}-[4-(trifluoromethyl)benzyl]amino}acetic acid

[(3-cyanobenzyl)({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)amino]-(oxo)acetic acid

[(4-chlorobenzyl)({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)amino]-(oxo)-acetic acid

{({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)[4-(trifluoromethyl)-benzyl]-amino}(oxo)acetic acid

{(3-cyanobenzyl)[(3'-{[(3-phenylpropyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

[(3-cyanobenzyl)({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino]-(oxo)acetic acid

[(4-chlorobenzyl)({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino]-(oxo)acetic acid

{({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)[4-(trifluoromethyl)-benzyl]-amino}(oxo)acetic acid

{benzyl[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}-(oxo)-acetic acid

{(3-cyanobenzyl)[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

{(4-chlorobenzyl)[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

oxo{[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoro-methyl)benzyl]amino}acetic acid

oxo{[(3'-{[(4-phenylbutyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoro-methyl)benzyl]amino}acetic acid

{(3-cyanobenzyl)[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

{(4-chlorobenzyl)[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

{[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

((4-chlorobenzyl){[3'-({[2-(4-methoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}amino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-methoxybenzyl)amino](oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[4-(methylsulfonyl)benzyl]amino}(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-methoxybenzyl)amino](oxo)acetic acid

{{3-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[6-(trifluoromethyl)-3-pyridinyl]methyl}-amino)-(oxo)acetic acid

4-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

({3-[(dodecylamino)carbonyl]benzyl}{4-[hydroxy(oxido)amino]benzyl}-amino)-(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(2-fluorobenzyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(2-pyridinylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(3-thienylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-hydroxybenzyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-phenoxybenzyl)amino](oxo)acetic acid

({3-[(dodecylamino)carbonyl]benzyl}{[6-(trifluoromethyl)-3-pyridinyl]methyl}-amino)-(oxo)acetic acid

3-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

5-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]-2-thiophene-carboxylic acid

({4-[(dodecylamino)carbonyl]benzyl}{4-[hydroxy(oxido)amino]-benzyl}-amino)(oxo)-acetic acid

((1,3-benzodioxol-5-ylmethyl){4-[(dodecylamino)carbonyl]-benzyl}amino)-(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-fluorobenzyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-phenoxybenzyl)amino](oxo)acetic acid

4-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

5-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]-2-thiophene-carboxylic acid

[{3-[(dodecylamino)carbonyl]benzyl}(2-thienylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(isopropyl)amino](oxo)acetic acid

((3,5-dichlorobenzyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[(3,5-dichlorobenzyl)(4-{[(3,3-diphenylpropyl)amino]carbonyl}-benzyl)amino]-(oxo)acetic acid

[(4-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]carbonyl}benzyl)(3,5-dichlorobenzyl)-amino]-(oxo)acetic acid

[(1,3-benzodioxol-5-ylmethyl)(4-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]carbonyl}-benzyl-amino](oxo)acetic acid

(2,3-dihydro-1H-inden-1-yl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{2,3-dihydro-1H-inden-1-yl[4-({[2-(4-phenoxyphenyl)ethyl]amino}-carbonyl)-benzyl]amino}(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-pyridinylmethyl)amino](oxo)acetic acid

([4-(dimethylamino)benzyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(3-pyridinylmethyl)amino](oxo)acetic acid

((4-cyanobenzyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(1,3-thiazol-2-ylmethyl)amino](oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-amino)(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-pyridinylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(3-pyridinylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(3-hydroxybenzyl)amino](oxo)acetic acid

((4-cyanobenzyl){3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(1,3-thiazol-2-ylmethyl)amino](oxo)acetic acid

({3-[(dodecylamino)carbonyl]benzyl}{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-amino)(oxo)acetic acid

((1,3-benzodioxol-5-ylmethyl){3-[(dodecylamino)carbonyl]-benzyl}amino)-(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-thienylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-pyridinylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(3-thienylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-hydroxybenzyl)amino](oxo)acetic acid

3-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

[cyclopentyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

[benzyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

(({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl){3-[hydroxy(oxido)amino]-benzyl}amino)(oxo)acetic acid

[({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(4-methoxybenzyl)amino]-(oxo)acetic acid

[({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(2-fluorobenzyl)amino](oxo)acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(methylsulfonyl)-benzyl]amino}-(oxo)acetic acid

[({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(4-phenoxybenzyl)amino]-(oxo)acetic acid

4-{[(carboxycarbonyl)({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)-amino]methyl}benzoic acid

(({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl){[6-(trifluoromethyl)-3-pyridinyl]methyl}amino)(oxo)acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[3-(trifluoromethyl)benzyl]amino}-(oxo)-acetic acid

[(3-chlorobenzyl)({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

{[(5-{[(3,3-diphenylpropyl)amino]sulfonyl}-2-thienyl)methyl][3-(trifluoromethyl)benzyl]-amino}(oxo)acetic acid

{(3-chlorobenzyl)[(5-{[(3,3-diphenylpropyl)amino]sulfonyl}-2-thienyl)methyl]amino}-(oxo)acetic acid

oxo{{[5-({[2-(4-phenoxyphenyl)ethyl]amino}sulfonyl)-2-thienyl]methyl}[3-(trifluoro-methyl)benzyl]amino}acetic acid

((3-chlorobenzyl){[5-({[2-(4-phenoxyphenyl)ethyl]amino}sulfonyl)-2-thienyl]methyl}-amino)(oxo)acetic acid

{[(5-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]sulfonyl}-2-thienyl)methyl][3-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

(({1-[(cyclohexylamino)carbonyl]-4-piperidinyl}methyl){4-[(dodecylamino)-carbonyl]-benzyl}amino)(oxo)acetic acid

([(1-{[4-(dimethylamino)anilino]carbonyl}-4-piperidinyl)methyl]{4-[(dodecylamino)-carbonyl]benzyl}amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[(1-hexanoyl-4-piperidinyl)methyl]-amino}(oxo)-acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[1-(3-iodobenzoyl)-4-piperidinyl]methyl}-amino)-(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[(1-{(2E)-3-[3-(trifluoromethyl)phenyl]-2-propenoyl}-4-piperidinyl)methyl]amino}(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[1-(2-quinoxalinylcarbonyl)-4-piperidinyl]-methyl}amino)(oxo)acetic acid

[({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)(4-{[(4-phenoxybenzyl)-amino]-carbonyl}benzyl)amino](oxo)acetic acid

[{[1-(3-iodobenzoyl)-4-piperidinyl]methyl}(4-{[(4-phenoxybenzyl)amino]-carbonyl}-benzyl)amino](oxo)acetic acid

oxo{(4-{[(4-phenoxybenzyl)amino]carbonyl}benzyl)[(1-{(2E)-3-[3-(trifluoromethyl)-phenyl]-2-propenoyl}-4-piperidinyl)methyl]amino}acetic acid

Intermediate compounds or prodrugs that may be transformed to give rise to the substituted methylene amide derivatives of formula (I) by hydrolysis are esters of the compounds of formulae (I-1) and (I-2) and include the following :

benzyl 4-({benzyl[ethoxy(oxo)acetyl]amino}methyl)benzoate

ethyl (benzyl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate

benzyl 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl]amino}methyl)benzoate

ethyl oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]-amino}acetate

ethyl {(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]amino}-(oxo)acetate

tert-butyl 4-{{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}piperidine-1-carboxylate

tert-butyl 4-{{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}piperidine-1-carboxylate

ethyl {{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetate

ethyl {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetate

tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)-acetyl]amino}-methyl)-piperidine-1-carboxylate

ethyl {{4-[(tert-butoxycarbonyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)-acetate

ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate

ethyl oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetate

ethyl [benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetate

ethyl (benzyl{4-[(tert-butoxycarbonyl)amino]benzyl}amino)(oxo)acetate

ethyl [(4-aminobenzyl)(benzyl)amino](oxo)acetate

ethyl oxo{[4-(trifluoromethyl)benzyl][4-(undec-10-enoylamino)benzyl]amino}acetate

ethyl oxo{{4-[(9E)-tetradec-9-enoylamino]benzyl}[4-(trifluoromethyl)benzyl]amino}-acetate

ethyl {benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetate

ethyl {{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)-acetate

ethyl oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]-amino}-acetate

ethyl {({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)[4-(trifluoromethyl)benzyl]-amino}(oxo)acetate

tert-butyl 4-({{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}-methyl)-piperidine-1-carboxylate

ethyl [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}methyl)amino](oxo)acetate

ethyl {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino}(oxo)acetate

ethyl (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate

ethyl [benzyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate

tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}methyl)-piperidine-1-carboxylate

ethyl [{4-[(dodecylamino)carbonyl]benzyl}(piperidin-4-ylmethyl)amino](oxo)acetate

ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate.

A further aspect of the present invention is the use of the compounds of formula (I) as medicament.

In particular, the compounds of formula (I) are useful for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity or polycystic ovary syndrome (PCOS).

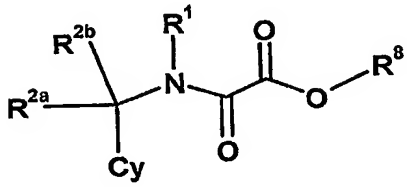
More specifically, compounds according to formula (I) are particularly useful for the treatment and/or prevention of diabetes type II.

The compounds according to formula (I) are suitable for the modulation of the activity of PTPs, in particular of PTP1B. It is therefore believed that the compounds of the present invention are therefore useful for the treatment and/or prevention of disorders which are mediated by PTPs, in particular of PTP1B. Said treatment involves the modulation – notably the down regulation or the inhibition - of PTPs, particularly of PTP1B.

Still a further object of the invention is a process for preparing substituted methylene amide derivatives according to formula I.

The substituted methylene amide derivatives of the present invention may be prepared from readily available starting materials using the below general methods and procedures. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions may also be used, unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

By the following set out general methods and procedures compounds of formula (Ia) are obtained.



(Ia)

The substituents of (Ia) are as above defined and R^8 is H, C_1-C_6 alkyl or 3-8 membered cycloalkyl group.

Generally, substituted methylene amide derivatives according to the general formula (I) may be obtained by several processes, using both solution-phase and solid-phase chemistry protocols. Depending on the nature of Cy, R^1, R^{2a}, R^{2b} and R^8, some processes will be preferred to others, this choice of the most suitable process being assumed by the practitioner skilled in the art.

Preparation using Solution Phase:

Generally, substituted methylene amide derivative of formula (I) may be obtained by the initial synthesis of the esters (Ia) and their subsequent hydrolysis to give rise to the substituted methylene amide derivative of the general formula (I).

a) Carboxamide and sulfonamide substituted methylene amide derivatives of formula (I)

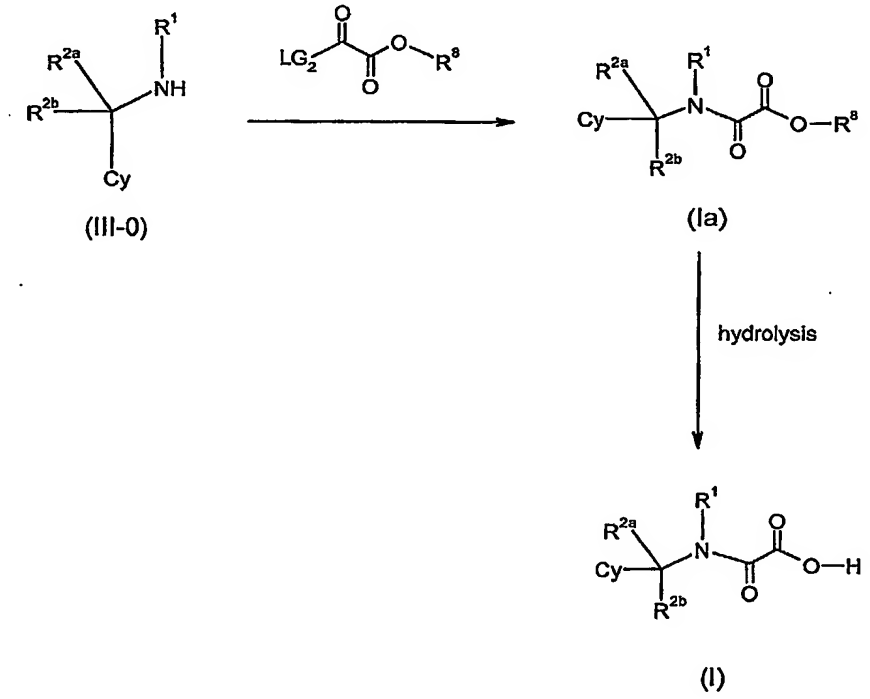
In the following the general preparation of carboxamide and sulfonamide substituted methylene amide derivatives of formula (I), wherein R^1, R^{2a}, R^{2b} and Cy are as above-defined, shall be illustrated (see Scheme A below).

Substituted methylene amide derivatives of formula (I) may be prepared by coupling the corresponding carboxylic acid derivatives (LG_2-CO-CO-R^8), wherein LG_2 is a suitable

leaving group - including Cl, N-hydroxy succinimide or benzotriazol-1-yl - and the primary or secondary amine Cy-$CR^{2a}R^{2b}$-NHR^1. Preparation of said amide derivatives is performed using conditions and methods well known to those skilled in the art to prepare an amide bond from an amine and a carboxylic acid or carboxylic acid derivative (e.g. acid chloride), with standard coupling agents, such as e.g. DIC, EDC, TBTU, DECP, DCC, PyBOP®, Isobutyl chloroformate or others in the presence or not of bases such as TEA, DIEA, NMM in a suitable solvent such as DCM, THF or DMF.

Substituted methylene amides of formula (Ia) are then submitted to hydrolysis using hydroxide (e.g. NaOH) and leading to the desired compounds of Formula (I).

Scheme A



General preparation according to the invention also includes compounds of Formula (I) in which Cy is particularly substituted by either –CO-$NR^3R^{3'}$, –NH-CO-R^3 or –SO_2-$R^3R^{3'}$ such as described in the schemes below, wherein R^3 and $R^{3'}$ are as above-

defined, and where chemical transformations of compounds of formula (Ia), also allow the obtention of compounds of formula (I).

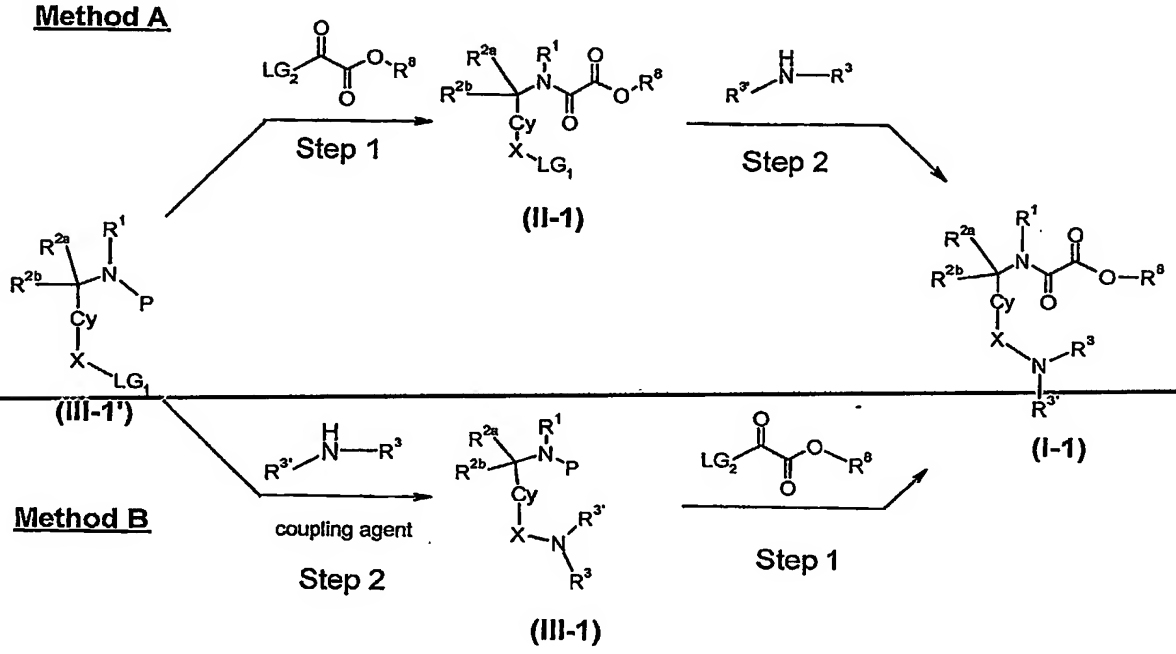
b) Carboxamide and sulfonamide substituted methylene amide derivatives of formula (I-1)

In the following the general preparation of carboxamide and sulfonamide substituted methylene amide derivatives of formula (I-1) - i.e. compounds of formula (I), wherein Cy is as above defined and is substituted by either $-CO-NR^3R^{3'}$ (X = -CO-) or $-SO_2-NR^3R^{3'}$ (X = $-SO_2-$) - shall be illustrated (see Scheme 1 below).

Substituted methylene amide derivatives of formula (I-1), wherein Cy is substituted with $-CO-NR^3R^{3'}$ may be prepared from the corresponding carboxylic derivatives (II-1), wherein LG_1 is a suitable leaving group - including OH, Cl, O-alkyl or O-alkylaryl and from a primary or secondary amine $-NHR^3R^{3'}$, wherein R^3, $R^{3'}$ being independently from each other selected from the group consisting of H, straight or branched (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2- C_6)alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl. A general protocol for such preparation is given below in the Examples (see Method A), using conditions and methods well known to those skilled in the art to prepare an amide bond from an amine and a carboxylic acid or carboxylic acid derivative (e.g. acid chloride), with standard coupling agents, such as e.g. DIC, EDC, TBTU, DECP, DCC, PyBOP®, Isobutyl chloroformate or others in the presence or not of bases such as TEA, DIEA, NMM in a suitable solvent such as DCM, THF or DMF.

Substituted methylene amides of formula (I-1), wherein Cy is substituted with $-SO_2-NR^3R^{3'}$ (X=$-SO_2-$) may also be prepared from the corresponding sulfonic acid derivatives (II-1), wherein LG_1 is a leaving group such as e.g. OH, Cl, O-Alkylaryl or O-Alkyl, and a primary or secondary amine $NHR^3R^{3'}$ (see Scheme 1; Method A).

Scheme 1



The carboxylic acid and sulfonic acid derivatives (II-1) (wherein X = -CO- or -SO_2-) may be obtained from the corresponding amine (III-1'), wherein P = H, by coupling with the ester as set out in Step 1. Thereby, LG_2 is a leaving group (e.g. Cl, N-hydroxy succinimide, benzotriazol-1-yl).

Said amines (III-1') in which P is H, may be obtained by deprotection of their corresponding protected form, wherein P is a protecting group such as e.g. Boc or Fmoc. For all the protection, deprotection methods, see Philip J. Kocienski, in "*Protecting Groups*", Georg Thieme Verlag Stuttgart, New York, 1994 and, Theodora W. Greene and Peter G. M. Wuts in "*Protective Groups in Organic Synthesis*", 3rd edition, John Wiley & Sons Inc., 1999 (NY).

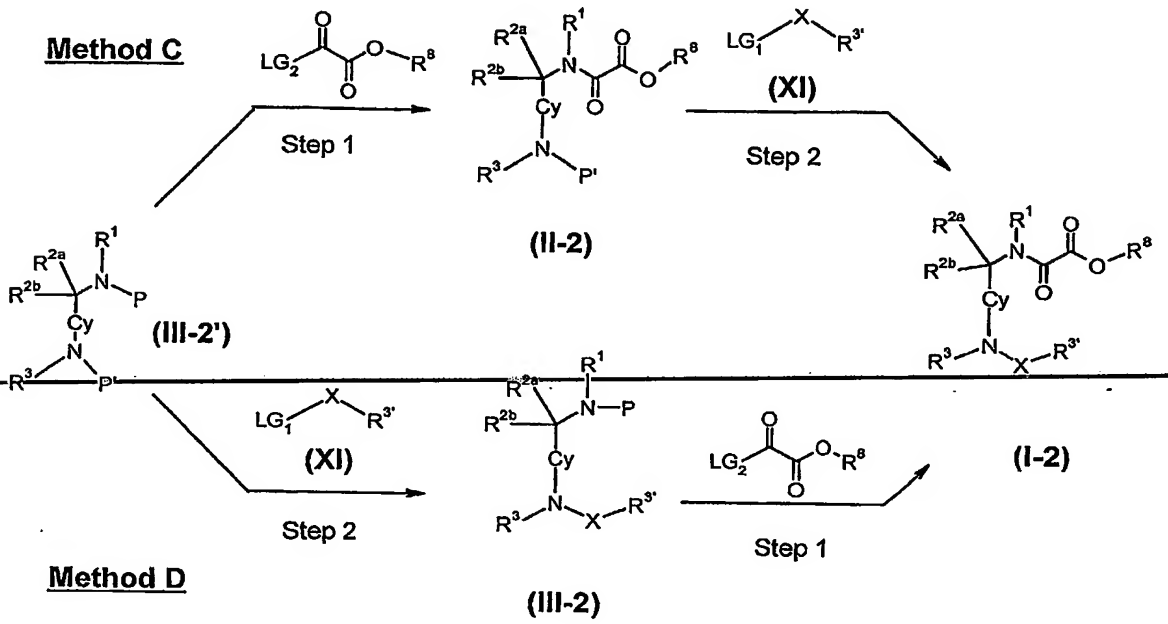
According to a further process, the substituted methylene amides of formula (I-1), wherein Cy is substituted with -CO-$NR^3R^{3'}$ or -$SO_2NR^3R^{3'}$ (X = -CO- or -SO_2-) may be prepared from the corresponding amines (III-1) by coupling with the ester LG_2-CO-CO-OR^8 wherein R^8 is an alkyl group and LG_2 is a leaving group such as for example Cl, N-hydroxy succinimide, or benzotriazol-1-yl, such as above-described in Scheme 1 (Method B).

Compounds (III-1), wherein P is H or any protecting groups such as Boc or Fmoc, may be prepared by addition of the corresponding carboxylic or sulfonic acid derivatives (III-1') (X=-CO-, X=-SO_2- respectively), whereby LG_1 is a leaving group such as e.g. OH, Cl or O-alkyl, with primary or secondary amines $NHR^3R^{3'}$ following solution-phase chemistry protocols such as described in the Examples and shown in Scheme 1 (Method B).

c) Substituted methylene amide derivatives of formula (I-2)

According to a further process, substituted methylene amide derivatives of formula (I-2), i.e. substituted methylene amide derivatives of formula (I), wherein Cy is substituted with -$NR^3COR^{3'}$ and R^3 and $R^{3'}$ are as above-defined, may be prepared from the corresponding amine (II-2), wherein P' is H, and LG_1-CO-$R^{3'}$ (XI) (X= -CO-) following the protocols described in the Examples and shown in Scheme 2 (Method C). LG_1 is a suitable leaving group such as e.g. Cl, OH or O-alkyl.

Scheme 2



The amines of formula (II-2) wherein P' is H, may be obtained by deprotection of their corresponding protected form, wherein P' is a protecting group such as e.g. Boc or Fmoc.

The amines of formula (II-2) wherein P' is H or any protecting groups such as Boc or Fmoc, may be obtained from the corresponding amine (III-2'), wherein P is H, by coupling with the ester as set out in Step 1. Thereby, LG_2 is a leaving group (e.g. Cl, N-hydroxy succinimide, benzotriazol-1-yl).

Said amines (III-2'), wherein P is H, may be obtained by deprotection of their corresponding protected form, wherein P is a protecting group such as e.g. Boc or Fmoc.

According to one embodiment, substituted methylene amide derivatives of formula (I-2), wherein Cy is as above-defined, may be substituted with $-NR^3COR^{3'}$ and may be prepared from the corresponding amines (III-2), wherein P is H, by coupling with the ester LG_2-CO-

$COOR^8$, wherein R^8 is C_1-C_6 alkyl, preferably ethyl or methyl, and LG_2 is a leaving group as above described (see Scheme 2 (Method D)).

Amines (III-2), wherein P is H, can be obtained by deprotection of their corresponding protected form, wherein P is a protecting group such as e.g. Boc or Fmoc.

Compounds (III-2), wherein P is H or any protecting groups such as Boc or Fmoc, are prepared by addition of the corresponding amines (III-2'), wherein P' is H, with derivatives of formula LG_1-CO-$R^{3'}$ (XI) (X= -CO-), whereby LG_1 is a suitable leaving group such as e.g. Cl, OH or O-alkyl following protocols described in the Examples and as shown above in Method D.

Compounds of formula (I-2) wherein X is different from the carbonyl functionality may be prepared by replacing compounds of formula (XI) with those containing the appropriate functional groups, e.g. sulfonyl chlorides, isocyanates, isothiocyanates, chloroformates, substituted alkyl halides, epoxides or others to yield sulfonamide, urea, thiourea, carbamate, substituted alkyl derivatives, substituted α,β-aminoalcools, or others, respectively.

d) Preparation of the precursor compounds of formula (I-3)

According to another process, substituted methylene amide derivatives of formula (I-3), i.e. substituted methylene amide derivatives of formula (I), wherein Cy is substituted with an oxadiazole (as an example for a heteroaryl) and R^3 is as above-defined, may be prepared from the corresponding acid derivative of formula (II-1), wherein LG_1 is a suitable leaving group such as e.g. Cl, OH or O-alkyl and imide oxime of formula (X) following protocols such as described in the Examples and shown in Scheme 3 (Method E). Thus, the starting acid derivatives of formula (II-1) are reacted with imide oxime of formula (X) using standard coupling agents, such as. DIC, EDC, TBTU, DECP, DCC, PyBOP®, Isobutyl

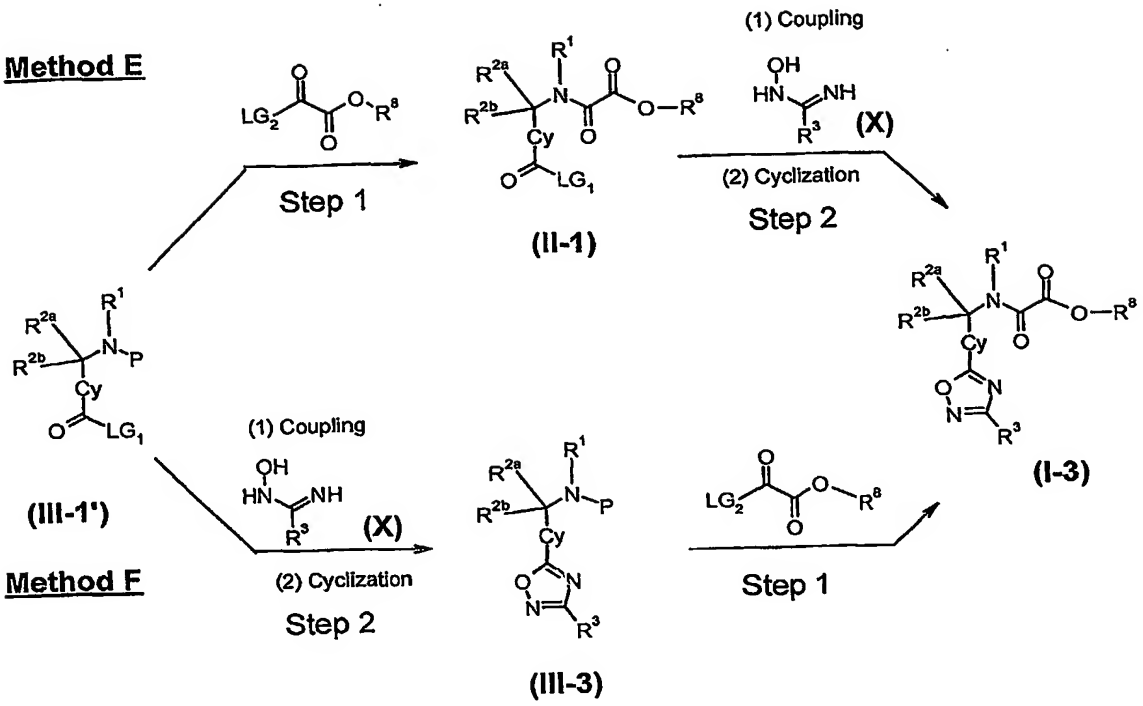
chloroformate or others in a suitable solvent such as DCM, followed by exposure to base, such as pyridine, to promote the cyclization yielding oxadiazole of formula (I-3).

According to an alternative process, the substituted methylene amides of formula (I-3) may be prepared from the corresponding amines (III-3) by coupling with the ester LG_2-CO-CO-OR^8 wherein R^8 is an alkyl or cycloalkyl group and LG_2 is a leaving group such as for example Cl, N-hydroxy succinimide, or benzotriazol-1-yl, such as described in Scheme 3 (Method F).

Compounds (III-3), wherein P is H, may be obtained by deprotection of their corresponding protected form, wherein P is a protecting group such as e.g. Boc or Fmoc.

Compounds (III-3), wherein P is H or any protecting groups such as Boc or Fmoc, may be prepared from their precursor of formula (III-1') and amide oxime of formula (X) following protocols such as described in the Examples and shown in Scheme 3 (Method F).

Scheme 3



e) Preparation of the precursor compounds of formula (III)

The precursor compounds of formulae (III), (including III-1', III-1, III-2', III-2 or III-3), mentioned in Schemes 1, 2 and 3, wherein Cy may be substituted with a moiety Q, like a substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, e.g. an oxadiazole, or a substituted or unsubstituted cycloalkyl moiety, or -CO-$NR^3R^{3'}$, -$COOR^3$, -$NP'R^3$, -$NR^3COR^{3'}$, -CO-LG_1, -SO_2-LG_1, -$SO_2NR^3R^{3'}$ may be prepared from the corresponding precursors of formulae (VII), (VIII) or (IX), using a variety of synthetic strategies for which some examples are indicated in the below Scheme 4.

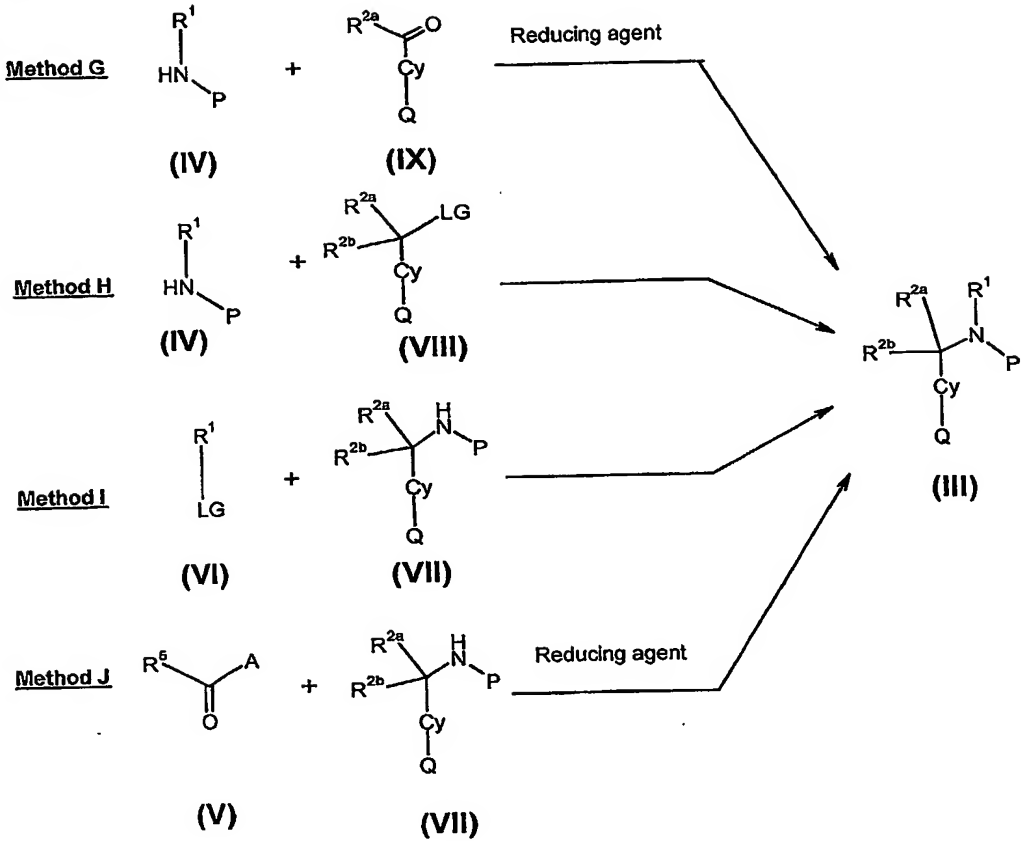
- Compounds of formula (III) – wherein R^{2b} is H - may for instance be prepared by alkylation of the amines (IV) - wherein R^1 is as above-defined and wherein P is H or a suitable protecting group such as e.g. Boc or Fmoc - with the carbonyl derivatives (IX), wherein R^{2a} is as above defined. The reaction (see Scheme 4, Method G) may be performed in the presence of a suitable reducing agent including $NaBH(OAc)_3$, $NaBH_3CN$, $NaBH_4$ or hydrogen and an appropriate catalyst such as Pd/C or Pt/C.

- Alternatively, compounds of formula (III) may be prepared by alkylation of amines of formula (IV) with the derivatives of formula (VIII), wherein LG is a suitable leaving group including Cl, Br, I, OH, OMs, OTs (see Method H). R^{2a} and R^{2b} are as above-defined.

- Also, compounds of formula (III) may be prepared by alkylation of amines of formula (VII), with the alkylating agents of formula (VI) wherein LG is the above-mentioned leaving group (Scheme 4, Method I).

- Still a further alternative is set out in Scheme 4, Method J. This embodiment illustrates the preparation of compounds of formula (III) by alkylation of the amines of formula (VII) with carbonyl derivatives (V) - wherein A is as above-defined - in the presence of a reducing agent such as e.g. $NaBH(OAc)_3$, $NaBH_3CN$, $NaBH_4$ or hydrogen with an appropriate catalyst such, as e.g. Pd/C or Pt/C, in order to provide compounds of formula (III), wherein R^1 is $-CH-R^5-A$ in which R^5 is selected from the group consisting of (C_1-C_{12})-alkyl, preferably (C_1-C_6)-alkyl, (C_2-C_{12})-alkenyl, (C_2-C_{12})-alkynyl, aryl, heteroaryl, (3-8-membered)cycloalkyl or heterocycloalkyl, (C_1-C_{12})-alkyl-aryl or (C_1-C_{12})-alkyl-heteroaryl, (C_2-C_{12})-alkenyl-aryl or -heteroaryl, (C_2-C_{12})-alkynyl-aryl or -heteroaryl.

Scheme 4



The precursor compounds of formulae (IV), (V), (VI), (VII), (VIII) or (IX) are either commercially available or readily accessible from commercial starting materials selected in the list mentioned in the list hereinafter:

(dl)-trans-2-benzyloxycyclopentylamine, 1-(1-naphthyl)ethylamine, 1,2,3,4-tetrahydro-1-naphthylamine, 1,2-dodecylene oxide , 1-aminoindane, 1-deoxy-1-(methylamino)glucitol, 2-amino-2-hydroxymethyl)-1,3-propanediol, 2-(2,4,6-trimethyl-phenyl)-ethylamine, 2-(3-chlorophenyl)ethylamine, 2-(3-methoxyphenyl)ethylamine, 2-(4-biphenyl)ethylamine, 2-(4-methoxyphenyl)ethylamine, 2,2-diphenylethylamine, 2-amino-1-methoxypropane, 2-

fluorobenzaldehyde, 2-formylthiazole, 2-morpholino-1,3-thiazole-5-carbaldehyde, 2-phenoxyphenethylamine, 2-phenylglycine ethyl ester hydrochloride, 2-pyridinecarboxaldehyde, 2-quinoxaloyl chloride, 2-thiophenecarboxaldehyde, 3-(benzyloxy)aniline, 3-(trifluoromethyl)benzaldehyde, 3,3-diphenylpropylamine, 3,5-dichlorobenzylamine, 3-aminophenyl trifluoromethyl sulfone, 3-carboxybenzaldehyde, 3-chlorobenzaldehyde, 3-cyanobenzaldehyde, 3-hydroxybenzaldehyde, 3-iodobenzoyl chloride, 3-nitrobenzaldehyde, 3-phenylbenzyl amine hydrobromide, 3-phenylpropylamine, 3-pyridinecarboxaldehyde, 3-thiophenecarboxaldehyde, 4-(1,2,3-thiadiazol-4-yl), benzylamine hydrochloride, 4-(aminomethyl)-1-N-Boc-aniline, 4-(dimethylamino)phenyl isocyanate, 4-(methylsulfonyl)benzaldehyde, 4-(trifluoromethyl)benzylamine, 4-amino-1-benzylpiperidine, 4-benzamidobenzylamine, 4-bromoaniline, 4-chloromethylbenzoyl chloride, 4-chlorobenzaldehyde, 4-cyanobenzaldehyde, 4-dimethylaminobenzaldehyde, 4-formyl-benzoic acid, 4-formyl-benzoic acid benzyl ester, 4-hydroxybenzaldehyde, 4-methoxybenzenesulfonyl chloride, 4-nitrobenzaldehyde, 4-n-pentylbenzylamine hydrochloride, 4-pentylbenzylamine hydrochloride, 4-phenoxyaniline, 4-phenoxybenzaldehyde, 4-phenoxybenzylamine, 4-phenoxyphenethylamine, 4-phenylbutylamine, 4-pyridinecarboxaldehyde, 4-tolyl boronic acid, 5-formyl-2-thiophenecarboxylic acid, 6-(trifluoromethyl)pyridine-3-carboxaldehyde, aniline, benzaldehyde, benzoylperoxide, benzylamine, chloro-oxo-acetic acid ethyl ester, cis-delta 9-trans-tetradecenoyl chloride, cyclohexyl isocyanate, cyclohexyl isocyanate, cyclopentanone, dl-3-amino-3-phenylpropionic acid, dl-alpha-methyl-benzylamine, dodecylamine, Fmoc-(3-aminomethyl)-benzoic acid, Fmoc-(4-aminomethyl)-benzoic acid, hexanoyl chloride, isopropylamine, lithium hydroxide monohydrate, l-phenylglycine t-butyl ester, methyl 4-formylbenzoate, N-bromo-succinimide, octylamine, p-anisaldehyde, pentadecylamine, piperonal, piperonylamine, sodium cyanoborohydride, sodium triacetoxyborohydride, tetrabutylammonium iodide, tetradec-9-enoyl chloride , tetrakis-triphenylphosphine palladium(0), thiophene-2-ethylamine, trans-2-phenylcyclopropylamine hydrochloride, trans-3-(trifluoromethyl)cinnamoyl chloride, tridecanoic acid, tridecanoyl chloride.

A preferred process for preparing compounds of formula (III) is set out in the above Scheme 4, Method G. Therein, the reductive amination of carbonyl compounds of formula (IX) wherein Q is -COO-Bn is performed with amines of formula (IV) and a reducing agent such as $NaBH_3(OAc)_3$ in a suitable solvent such as DCE or THF. The process thus affords the amine of formula (III), wherein Q is C(O)OBn.

According to the methods described in Scheme 1 (Method A), the resulting amine (III) is coupled with an ester LG_2-CO-COO-R^8, wherein R^8 is a C_1-C_6 alkyl or cycloalkyl, preferably ethyl or methyl, and LG_2 is a leaving group such as e.g. Cl, in the presence of a base such as DIEA in an aprotic solvent (such as e.g. DCM or THF), thus affording substituted methylene amide derivatives of formula (II-1). Subsequent benzyl deprotection using standard H_2/Pd methods and followed by the coupling of the resulting acid, wherein X is CO and LG_1 is -OBn, with amines -$NHR^3R^{3'}$, with using standard carbodiimide - or standard mixed anhydride - mediated methods affords the desired compounds of formula (I-1), wherein R^8 is ethyl or methyl (see Scheme 1). The latter compounds may be hydrolysed to yield compounds of formula (Ia) of this invention, wherein R^8 is H, by their treatment with hydroxide such as e.g. NaOH in an appropriate protic solvent (such as e.g. EtOH), followed by acidification of the reaction mixture.

According to a further preferred process of preparing compounds of formula (Ia), carbonyl derivatives of formula (IX) (see Scheme 4), wherein Q is -$CONR^3R^{3'}$ may be prepared from their commercially available or readily accessible from Fommercial starting materials precursor in which Q is -COOH and amines $HNR^3R^{3'}$ using standard carbodiimide- or standard mixed anhydride-mediated methods. The reductive amination of the carbonyl derivatives of formula (IX) wherein Q is -$CONR^3R^{3'}$ with amines of formula (IV) and a reducing agent such as $NaBH(OAc)_3$ in a suitable solvent such as DCE or THF affords the amine of formula (III) wherein Q is -$CONR^3R^{3'}$, following the methods described in Method G, Scheme 4. The resulting amine (III) is coupled with the ester LG_2-CO-COO-R^8, wherein R^8 is a C_1-C_6 alkyl or cycloalkyl, preferably ethyl or methyl, and LG_2 is a leaving

group such as e.g. Cl, in the presence of a base such as DIEA in an aprotic solvent (such as e.g. DCM or THF) affording the ester (I-1). The latter compounds may be hydrolysed to compounds of formula (Ia) of this invention, wherein R^8 is H, by their treatment with hydroxide such as e.g. NaOH in an appropriate protic solvent (such as e.g. EtOH), followed by acidification of the reaction mixture.

Basic salts of the compounds of formula (I) are prepared in a conventional manner as is known by a person skilled in the art. In particular the Me-D-glucamine and the tromethamine (2-amino-2-(hydroxymethyl)-1,3-propandiol) salts of this invention provide water-soluble derivatives for improved bioavailability.

The methods of preparation of the substituted methylene amides of formula (I) of this invention according to the above protocols have the specific advantage of being convenient and economic in the sense that they involve only a few steps.

f) Preparation using Solid-Phase and/or mixed solid/solution phase:

According to yet another general approach, substituted methylene amides according to the general formula (Ia), wherein the substituents R^1, R^{2a}, R^{2b} and Cy are as above defined, may be prepared by solid-phase and/or mixed solid/solution-phase synthesis protocols such as those described in the examples and shown in Schemes 1, 2, 3 and 4 above using well known technical approaches (such as IRORI®). It will be appreciated by the practitioner skilled in the art that basically the same conditions, methods and reagents as above described in Schemes 1, 2, 3 and 4 for the solution-phase synthesis of compounds of formula (Ia) could be applied to the solid-phase and/or mixed solid-/solution-phase synthesis of said compounds. In the context of such a solid-phase and/or mixed solid-solution-phase synthesis protocol, R^3 is as above-defined. Cleavage from the resin is effected under acidic conditions, affording the corresponding substituted methylene amide derivatives of formula (Ia). It is to be understood that further to the resin types mentioned in the Examples such as e.g. Sasrin aldehyde resins, other suitable reagents, notably resins,

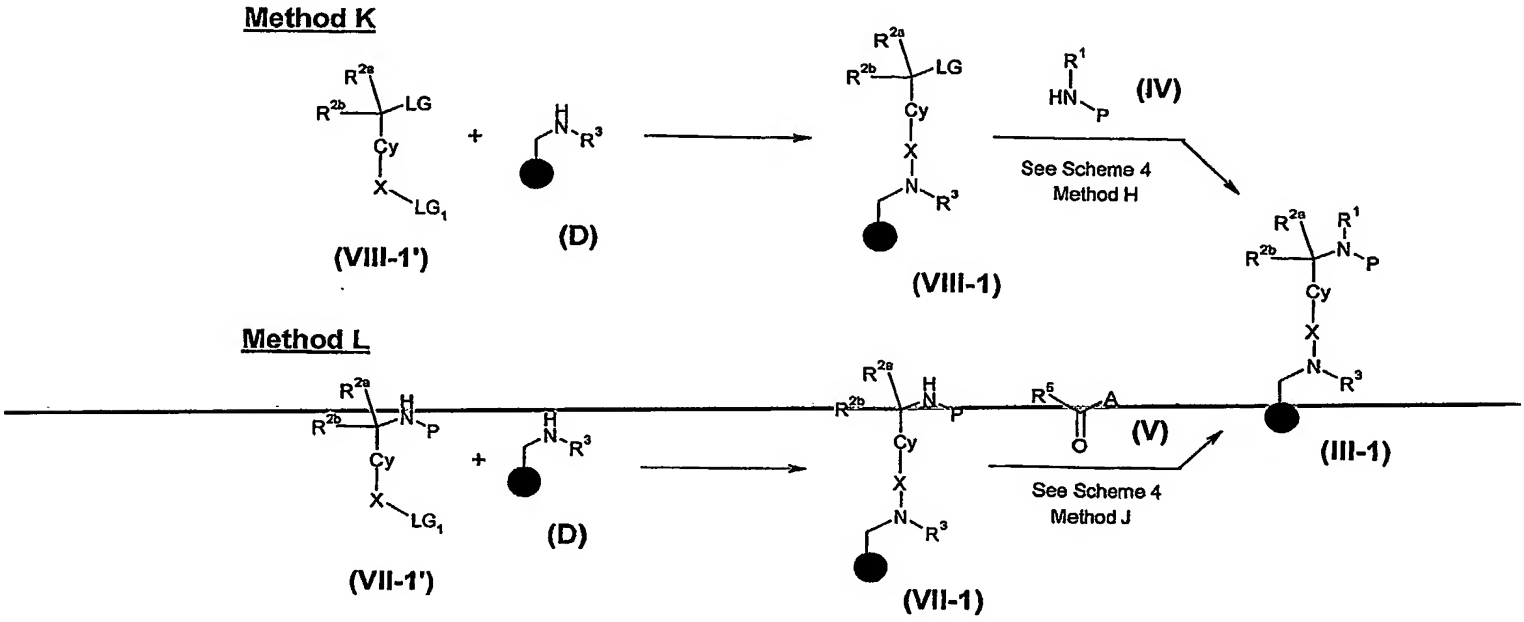
known to a person skilled in the art, could be employed for the solid-phase synthesis of compounds of general formula (Ia).

The filled circles in the below Scheme 5 illustrate the resin beads to which the compounds are linked during the solid phase synthesis.

In one particularly preferred process, resin-bound amines of formula NHR^3R^6 (D), wherein R^6 represents any suitable resin (Scheme 5) and R^3 is above-defined in the description, are prepared from commercially available *per se* or readily accessible from resins such as e.g. Sasrin aldehyde or bromo-Wang resins and amines, using standard reductive amination or alkylation conditions well known to the practitioner skilled in the art. The resin-bound amines NHR^3R^6 (D) may then be acylated with compounds of formula (VIII-1') wherein X is –CO- and LG_1 is Cl in the presence of base such as e.g. DIEA, in suitable solvent such as NMP or DCM; or X may also be is $-SO_2-$ and LG_1 is Cl using standard conditions involving a base such as DIEA in an aprotic solvent such as DCM or THF affording compounds of formula (VIII-1) (Scheme 5, Method L).

According to the methods outlined in Scheme 4 (Method H), the displacement of the leaving group LG from the latter resin-bound intermediates (VIII-1) by their reaction with amines $NHPR^1$ (IV) in the presence of iodide such as TBAI or NaI in a suitable solvent such as e.g. NMP at suitable temperature such as 80°C can afford resin-bound compounds of Formula (III-1). Finally, this compounds is coupled with the ester LG_2-CO-COO-R^8, wherein R^8 is preferably ethyl or methyl and LG_2 is a leaving group such as e.g. Cl, in the presence of a base such as DIEA in an aprotic solvent (such as e.g. DCM or THF) affording the resin-bound ester (I-1). The latter compounds can be hydrolysed to compounds of formula (Ia) of this invention, wherein R^8 is H, by their treatment with hydroxide such as e.g. NaOH in an appropriate solvent (such as e.g. THF). Cleavage from the resin is performed under acidic conditions (such as e.g. a DCM solution containing 20 % TFA), affording the corresponding desired substituted methylene amide derivatives of Formula (Ia).

Scheme 5



In one other preferred synthetic approach (Method L), the resin-bound amines of formula NHR^6R^3 (D), wherein R^6 represents a suitable resin (Scheme 5) can be acylated with compounds of formula (VII-1'), wherein X is -CO-, LG_1 is OH, R^1, R^{2a}, R^{2b}, R^3 and R^5 are as above-defined and P is a protecting group such as Fmoc or Pht, using standard conditions involving a coupling reagent such as e.g. PyBOP®, in a suitable solvent such as NMP or DCM affording resin-bound compounds of formula (VII-1). The same resin-bound amines of formula NHR^6R^3 can be sulfonylated with compounds of formula (VII-1'), wherein X is $-SO_2-$, LG_1 is Cl and P is a protecting group such as Fmoc or Pht, using standard conditions involving a base such as DIEA affording resin-bound compounds of formula (VII-1). These latter intermediates can be deprotected following standard conditions and then alkylated following the methods outlined in Scheme 4 (Method J) to afford the compounds of formula (III-1). Finally, these compounds are converted to the

desired substituted methylene amides of formula (Ia), following the methods described above.

When employed as pharmaceuticals, substituted methylene amide derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, substituted methylene amide derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the substituted methylene amide derivative according to the invention is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, substituted methylene amide derivatives of formula (I) in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 8 of *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein be reference.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences.*

In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention. The following abbreviations are hereinafter used in the accompanying examples: min (minute), h (hour), g (gram), mg (milligram), mmol (millimole), m.p. (melting point), eq (equivalents), mL (milliliter), µL (microliters), mL (milliliters), APCI (Atmospheric pressure chemical ionization), ESI (Electro-spray ionization), L (liters), AcOEt (Ethyl acetate), Boc (tert-Butoxycarbonyl), CH_3CN (Acetonitrile), DBU (Diazabicyclo [5.4.0]undec-7-ene), DCC (Dicyclohexyl carbodiimide), DCE (Dichloroethane), DIEA (Diisopropylethylamine), Fmoc (9-Fluorenylmethoxycarbonyl), $CDCl_3$ (deuterated chloroform), c-Hex (Cyclohexanes), DCM (Dichloromethane), DIC (Diisopropyl carbodiimide), DMAP (4-Dimethylaminopyridine), DMF (Dimethylformamide), DMSO (Dimethylsulfoxide), DMSO-d_6 (Deuterated dimethylsul-foxide), EDC (1-(3-Dimethyl-amino-propyl)-3-ethylcarbodiimide), EtOAc (Ethyl acetate), Et_2O (Diethyl ether), EtOH (Ethanol), HOBt (1-Hydroxybenzotriazole), K_2CO_3 (Potassium carbonate), MeOH (Methanol), CD_3OD (Deuterated methanol), $MgSO_4$ (Magnesium sulfate), NaH (Sodium hydride), $NaHCO_3$ (Sodium bicarbonate), $NaBH_3CN$ (Sodium cyanoborohydride), $NaBH_4$ (Sodium borohydride), $NaBH(OAc)_3$ (Sodium triacetoxyborohydride), NMM (N-methyl-morpholine), NMP (N-Methylpyrrolidone), nBuLi (n-Butyl-lithium), $Pd(PPh_3)_4$ (Tetrakis triphenylphosphine palladium), PetEther (Petroleum ether), Pht (Phtalimide), PyBOP®

(Bentotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate), rt (room temperature), SPE (solid phase extraction), TEA (Triethylamine), TFA (Trifluoro-acetic acid), THF (Tetrahydrofuran), TBTU (2-(1-H-benzotriazole-1-yl)-1,1,3,3-tetramethyluromium tetrafluoroborate).

The HPLC, MS and NMR data provided in the examples described below were obtained as followed. HPLC: Waters Symmetry C_8 column 50 mm x 4.6 mm; UV detection at 254 nm; flow: 2 mL/min; Conditions A: 8 min gradient from 0.1 % TFA in H_2O to 0.07 % TFA in CH_3CN; Conditions B: 10 min gradient from 0.1 % TFA in H_2O to 0.07 % TFA in CH_3CN. The semi-preparative reverse-phase HPLC was obtained as followed: Supelcosil ABZ+Plus column (25 cm x 21.2 mm, 12 µm); UV detection at 254 nm and 220 nm; flow 20 mL/min; Condition C: 10 min gradient from 30 % CH_3CN in 0.1 % TFA in CH_3CN to 100 % CH_3CN followed by 5 min elution at 100 % CH_3CN. The MS data provided in the examples described below were obtained as followed: Mass spectrum: PE sciex API 150 EX (APCI or ESI) or LC/MS Waters ZMD (ESI). The NMR data provided in the examples described below were obtained as followed: ^{1}H-NMR: Bruker DPX-300MHz.

Examples

Example 1: (benzyl{4-[(dodecylamino)carbonyl] benzyl}amino) (oxo)acetic acid

Step a) Formation of the secondary amine of formula (III) following the Method G (See Scheme 4), e.g. 4-(benzylamino-methyl)-benzoic acid benzyl ester

To a solution of 4-formyl-benzoic acid benzyl ester (5.00 g, 20.81 mmol) (compound described *in Bioorg. Med.Chem.*; 5; 9; 1873-82 (1997)) and benzyl amine (2.453 g, 22.89 mmol) in DCE (150 mL) was added at once $NaBH(OAc)_3$ (6.175 g, 29.14 mmol) and the resulting mixture was stirred overnight at rt. 30 mL of a saturated aqueous solution of $NaHCO_3$ were added to the reaction mixture, the aqueous layer was separated and extracted with DCM (3x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column

chromatography over silica gel (AcOEt/c-Hex 4/1 to 1/1 in about 1h) to give the title compound as a colorless oil (4.780 g, 69 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 2H), 7.37-7.16 (m, 12H), 5.27 (s, 2H), 3.77 (s, 2H), 3.70 (s, 2H)

M^+(ESI): 332.2

HPLC (Condition B), Rt: 4.26 min (HPLC purity: 98.5 %).

Step b) Formation of the oxamic ester of formula (II-1) following the Method A (See Scheme 1), e.g. 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid benzyl ester

To a solution of 4-(benzylamino-methyl)-benzoic acid benzyl ester (4.50 g, 13.58 mmol) and TEA (2.748 g, 27.16 mmol) in anhydrous THF (100 mL) at 0°C under inert atmosphere, was added dropwise the chloro-oxo-acetic acid ethyl ester (2.781 g, 20.37 mmol) diluted in THF (10 mL). The reaction mixture was stirred at 0°C for 2 h. The solvent was evaporated and 100 mL of DCM were added. 20 mL of a saturated aqueous solution of $NaHCO_3$ were added and the aqueous layer was separated and extracted with DCM (3x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 4/1 to 2/1 in about 1h) to give the title compound as a colorless oil (5.810 g, 99 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 2H), 7.37-7.11 (m, 12H), 5.30 (s, 2H), 4.44 (m, 2H), 4.31-4.22 (m, 4H), 1.22 (t, J=7.5 Hz, 3H)

M^+(APCI): 432.0

HPLC (Condition B), Rt: 7.2 min (HPLC purity: 99.4 %).

Step c) Formation of the oxamic ester of formula (II-1), e.g. 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid

H_2 (1 atm) was bubbled slowly trough a suspension of 10 % Pd/C (300 mg) in EtOH (50 mL) for 15 min at rt. To this suspension was then added a solution of 4-[(benzyl-

ethoxyoxalyl-amino)-methyl]-benzoic acid benzyl ester (5.500 g, 12.75 mmol) diluted in 15 mL of EtOH. The resulting reaction mixture was stirred under H_2 (1 atm) for 5 h at rt. The reaction mixture was filtered over a pad of celite to remove the catalyst. The solvent was evaporated to afford the title compound as a colorless oil used in the next steps without further purification (4.217 g, 97 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (m, 2H), 7.37-7.11 (m, 7H), 4.51 (m, 2H), 4.39-4.30 (m, 4H), 1.27 (m, 3H)

M^-(APCI): 340.0; M^+(APCI): 342.0

HPLC (Condition A), Rt: 4.31 min (HPLC purity: 99.1 %).

Step d) Formation of the oxamic ester of formula (I-1) following the Method A (See Scheme 1), e.g. ethyl (benzyl{4-[(dodecylamino)carbonyl]benzyl}amino) (oxo) acetate, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

To a solution of 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid (1500 mg, 4.39 mmol) in anhydrous THF (15 mL) at RT was added EDC (1.261 g, 6.58 mmol) and dodecylamine (1.018 g, 5.49 mmol) under inert atmosphere. The resulting mixture was stirred overnight at rt. The solvent was evaporated and the residue dissolved in DCM (30 mL) and washed with a 1N aqueous solution of HCl (2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a colorless oil. This crude product was purified by column chromatography over silica gel (AcOEt/ c-Hex 3/1 to 1/1 in about 15 min) to give the title compound as a colorless oil (500 mg, 22 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (m, 2H), 7.37-7.26 (m, 7H), 6.09 (br s, 1H), 4.5 (m, 2H), 4.36-4.30 (m, 4H), 3.45 (m, 2H), 1.62 (m, 3H), 1.36-1.27 (m, 20H), 0.88 (m, 3H)

M^-(ESI): 507.2

HPLC (Condition A), Rt: 6.98 min (HPLC purity: 99.9 %).

Step e) Formation of the oxamic acid of formula (I), e.g. (benzyl{4-[(dodecylamino)-carbonyl]benzyl}amino)(oxo)acetic acid

To a solution of ethyl (benzyl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo) acetate (690 mg, 1.36 mmol) in EtOH (4 mL) was added a 1N aqueous solution of NaOH (1.36 mL, 1.36 mmol) and the resulting reaction mixture was stirred at rt for 2 h. The solvents were evaporated and the residue dissolved in EtOAc (20 mL) and washed with a 1N aqueous solution of HCl (5 mL). The aqueous layer was separated and washed with EtOAc (2x 10mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound as a white solid (603 mg, 93 %).

^1H NMR (CD_3OD, 300 MHz) δ 7.80 (m, 2H), 7.45-7.28 (m, 6H), 7.22 (m, 1H), 4.54 (s, 2H), 4.50 (s, 2H), 3.38 (t, 2H, J=6.5 Hz), 1.64 (m, 2H), 1.38-1.21 (m, 18H), 0.88 (t, 3H, J=6.6 Hz)

M^-(ESI): 479.2

HPLC (Condition A), Rt: 6.01 min (HPLC purity: 98.6 %).

Analysis calculated for $C_{29}H_{40}N_2O_4$: C, 72.47; H, 8.39 ; N, 5.83 %. Found: C, 72.30; H, 8.36 ; N, 5.79 %

Example 2: (benzyl{4-[(dodecylamino)carbonyl] benzyl}amino)(oxo)acetic acid, tromethamine (2-amino-2-hydroxymethyl)-1,3-propanediol) salt

A mixture of (benzyl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid (1.842 g, 3.83 mmol), tris (hydroxymethyl)amino methane (0.464 g, 3.83 mmol) and EtOH (38 mL) were heated until a homogeneous solution was obtained. The solvent was removed *in vacuum* and the residue was dissolved in a 9/1 mixture of H_2O/EtOH. The resulting solution was then lyophilized to afford the title compound as a fluffy white powder (2.299 g, 99 %).

M^-(LC/MS(ESI)): 479.5; M^+(LC/MS(ESI)): 481.3

HPLC (Condition A), Rt: 6.0 min (HPLC purity: 98.6 %).

Analysis calculated for $C_{29}H_{40}N_2O_4.C_4H_{11}NO_3$: C, 65.86; H, 8.54; N, 6.98 %. Found: C, 65.10; H, 8.78; N, 6.90 %

Example 3: (benzyl{4-[(dodecylamino)carbonyl] benzyl}amino)(oxo)acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt

The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine gave the title compound as a white solid (89 %)
M^-(LC/MS(ESI)): 479.3; M^+(LC/MS(ESI)): 481.3
HPLC (Condition A), Rt: 6.1 min (HPLC purity: 99.25 %).
Analysis calculated for $C_{29}H_{40}N_2O_4.C_7H_{17}NO_5 \cdot 1.2\ H_2O$: C, 61.99; H, 8.24; N, 6.02 %.
Found: C, 61.84; H, 8.60; N, 5.99 %

Example 4: oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl] amino}acetic acid

Step a) Formation of benzyl 4-({[4-(trifluoromethyl)benzyl]amino}methyl)benzoate.
The same procedure as employed in the preparation of Example 1 (step a) but using 4-trifluoromethyl-benzylamine gave the title compound as a yellow oil (74 %).
M^+(LC/MS(ESI)): 400.3
HPLC (Condition A), Rt: 3.76 min (HPLC purity: 97.6 %).

Step b) Formation of benzyl 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl] amino}methyl)benzoate
The same procedure as employed in the preparation of Example 1 (step b) but using the benzyl 4-({[4-(trifluoromethyl)benzyl]amino}methyl)benzoate gave the title compound as a colorless oil (95 %).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (t, 2H, J=8.3 Hz), 7.48 (m, 2H), 7.37-7.13 (m, 9H), 5.25 (br s, 2H), 4.41 (br s, 2H), 4.27-4.18 (m, 4H), 1.20 (t, 3H, J=7.0 Hz)
M^-(LC/MS(ESI)): 498.1; M^+(LC/MS(ESI)): 500.3
HPLC (Condition A), Rt: 6.14 min (HPLC purity: 98.9 %).

Step c) Formation of 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl]amino}methyl)-benzoic acid

The same procedure as employed in the preparation of Example 1 (step c) but using benzyl 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl]amino}methyl)benzoate gave the title compound as a colorless foam (84 %).

M^-(LC/MS(ESI)): 408.2; M^+(LC/MS(ESI)): 410.1

HPLC (Condition A), Rt: 4.43 min (HPLC purity: 98.9 %).

Step d) Formation of ethyl oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}acetate

The same procedure as employed in the preparation of Example 1 (step d) but using 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl]amino}methyl)benzoic acid gave the title compound as a white solid (78 %).

M^-(ESI): 617.2

HPLC (Condition A), Rt: 7.54 min (HPLC purity: 97.7 %).

Step e) Formation of the oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)-benzyl] amino}acetic acid

The same procedure as employed in the preparation of Example 1 (step e) but using the ethyl oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}-acetate gave the title compound as a colorless foam (84 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.77 (m, 2H), 7.58 (m, 3H), 7.44 (d, 1H, J=8.3 Hz), 7.38 (d, 1H, J=8.3 Hz), 7.30 (d, 1H, J=8.3 Hz), 4.56-4.50 (m, 4H), 3.37 (t, 2H, J=7.2 Hz), 1.64 (m, 2H), 1.30 (m, 24H), 0.91 (t, 3H, J=6.6 Hz)

M^-(LC/MS(ESI)): 589.1; M^+(LC/MS(ESI)): 591.1

HPLC (Condition A), Rt: 7.25 min (HPLC purity: 98.1 %).

Example 5: (benzyl{4-[(pentadecylamino)carbonyl] benzyl}amino) (oxo)acetic acid

Step a) Formation of the secondary amine of formula (III) following the Method G (See Scheme 4), e.g. 4-(benzylamino-methyl)-benzoic acid benzyl ester

To a solution of 4-formyl-benzoic acid benzyl ester (5.00 g, 20.81 mmol) and benzyl amine (2.453 g, 22.89 mmol) in DCE (150 mL) was added at once $NaBH(OAc)_3$ (6.175 g, 29.14 mmol) and the resulting mixture was stirred overnight at rt. 30 mL of a saturated aqueous solution of $NaHCO_3$ were added to the reaction mixture, the aqueous layer was separated and washed with DCM (3x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 4/1 to 1/1 in about 1h) to give the title compound as a colorless oil (4.780 g, 69 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 2H), 7.37-7.16 (m, 12H), 5.27 (s, 2H), 3.77 (s, 2H), 3.70 (s, 2H)

M^+(ESI): 332.2

HPLC (Condition B), Rt: 4.26 min (HPLC purity: 98.5 %).

Step b) Formation of the oxamic ester of formula (II-1) following the Method A (See Scheme 1), e.g. of the 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid benzyl ester

To a solution of 4-(benzylamino-methyl)-benzoic acid benzyl ester (4.50 g, 13.58 mmol) and TEA (2.748 g, 27.16 mmol) in anhydrous THF (100 mL) at 0°C under inert atmosphere, was added dropwise the chloro-oxo-acetic acid ethyl ester (2.781 g, 20.37 mmol). The reaction mixture was stirred at 0°C for 2 h. Most of the solvents were evaporated and 100 mL of DCM were added. 20 mL of a saturated aqueous solution of $NaHCO_3$ were added to the reaction mixture, the aqueous layer was separated and extracted with DCM (3x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column

chromatography over silica gel (AcOEt/c-Hex 4/1 to 2/1 in about 1h) to give 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid benzyl ester as a colorless oil (5.810 g, 99 %).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m, 2H), 7.37-7.11 (m, 12H), 5.30 (s, 2H), 4.44 (m, 2H), 4.31-4.22 (m, 4H), 1.22 (m, 3H)
M^+(APCI): 432.0
HPLC (Condition B), R_t: 7.2 min (HPLC purity: 99.4).

Step c) Formation of the of the oxamic ester of formula (II-1), e.g. 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid

H_2 (1 atm) was bubbled slowly trough a suspension of 10 % Pd/C (300 mg) in EtOH (50 mL) for 15 min at rt. To this suspension was then added a solution of 4-[(benzyl-ethoxy-oxalyl-amino)-methyl]-benzoic acid benzyl ester (5.500 g, 12.75 mmol) diluted in 15 mL of EtOH. The resulting reaction mixture was stirred under 1 atm H_2 for 5 h at rt. The reaction mixture was filtered over a pad of celite to remove the catalyst. EtOH was evaporated to afford the title compound as a colorless oil used in the next steps without further purification (4.217 g, 97 %).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (m, 2H), 7.37-7.11 (m, 7H), 4.51 (m, 2H), 4.39-4.30 (m, 4H), 1.27 (m, 3H)
M^-(APCI): 340.0; M^+(APCI): 342.0
HPLC (Condition A), Rt: 4.31 min (HPLC purity: 99.1 %).

Step d) Formation of the oxamic ester of formula (I-1) following the Method A (See Scheme 1), e.g. ethyl (benzyl{4-[(pentadecylamino)carbonyl] benzyl}amino)(oxo) acetate, using supported cyclohexylcarbodiimide

To a solution of 4-[(benzyl-ethoxyoxalyl-amino)-methyl]-benzoic acid (102 mg, 0.3 mmol) and pentadecylamine (39.9 mg, 0.2 mmol) in DCM (2 mL), the N-cyclohexylcarbodiimide, N-methyl polystyrene HL (Novabiochem, 355 mg, 0.6 mmol, loading: 1.69 mmol/g) was

added at once the and the resulting reaction mixture was stirred overnight at rt. The resin was filtered and the solvents were evaporated under vacuum to afford a colorless oil. This crude product was purified by column chromatography over silica gel (EtOAc) to give the title compound as a colorless oil (39 mg, 35 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (m, 2H), 7.37-7.26 (m, 7H), 6.13 (br s, 1H), 4.5 (m, 2H), 4.36-4.30 (m, 4H), 3.45 (m, 2H), 1.62 (m, 2H), 1.36-1.27 (m, 26H), 0.88 (t, J= 8.0 Hz, 3H)

M^-(APCI): 549.1; M^+(APCI): 551.4

HPLC (Condition A), Rt: 7.46 min (HPLC purity: 98.2 %).

Step e) Formation of the oxamic acid of formula (I-1), e.g. (benzyl{4-[(pentadecylamino)-carbonyl]benzyl}amino)(oxo)acetic acid

To a solution of ethyl (benzyl{4-[(pentadecylamino)carbonyl]benzyl}amino)(oxo) acetate (28.0 mg, 0.051 mmol) in EtOH (1 mL) was added NaOH (14.9 mg, 0.37 mmol) dissolved in H_2O (0.37 mL) and the resulting reaction mixture was stirred at rt for 2 h. The solvents were evaporated then EtOAc (5 mL) and a 1N aqueous solution of HCl (1 mL) were added to the residue. The aqueous layer was separated and extracted with EtOAc (2x 5mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a white solid (27.5 mg, 96 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.70 (m, 2H), 7.37 (d, 1H, J=8.3 Hz), 7.30-7.10 (m, 6H), 4.39 (m, 4H), 3.26 (t, 2H, J=7.0 Hz), 1.54 (m, 2H), 1.26 (m, 24H), 0.90 (t, J=7.5 Hz, 3H)

M^-(APCI): 521.6

HPLC (Condition A), Rt: 6.96 min (HPLC purity: 98.4 %).

Example 6: (benzyl{4-[(tridecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

Step a) Formation of ethyl (benzyl{4-[(tridecylamino)carbonyl] benzyl}amino)(oxo) acetate

The same procedure as employed in the preparation of Example 5, step d, but using tridecylamine gave the title compound as a colorless oil (40 %)
M^-(APCI): 523.2; M^+(APCI): 521.2
HPLC (Condition A), Rt: 7.06 min (HPLC purity: 99.2 %).

Step b) Formation of (benzyl{4-[(tridecylamino)carbonyl]benzyl}amino)(oxo)acetic acid
The same procedure as employed in the preparation of Example 5, step e, but using the ethyl (benzyl{4-[(tridecylamino)carbonyl] benzyl}amino)(oxo) acetate gave the title compound as a white solid (94 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.73 (m, 2H), 7.40 (m, 1H), 7.29-7.16 (m, 6H), 4.45-4.36 (m, 4H), 3.34 (t, 2H, J=7.2 Hz), 1.57 (m, 2H), 1.30-1.23 (m, 20H), 0.84 (t, 3H, J=6.6 Hz)
M^-(APCI): 493.2
HPLC (Condition A), Rt: 6.47 min (HPLC purity: 99.6 %).

Example 7: [benzyl(4-{[dodecyl(methyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

Step a) Formation of ethyl (benzyl{4-[(tridecylamino)carbonyl] benzyl}amino)(oxo) acetate
The same procedure as employed in the preparation of Example 5, step d, but using dodecyl-methyl-amine gave the title compound as a colorless oil (54 %).
HPLC (Condition A), Rt: 7.13 min (HPLC purity: 92.5 %).

Step b) Formation of [benzyl(4-{[dodecyl(methyl)aminocarbonyl}benzyl) amino](oxoacetic acid
The same procedure as employed in the preparation of Example 5, step e, but using the ethyl (benzyl{4-[(tridecylamino)carbonyl] benzyl}amino)(oxo) acetate gave the title compound as a colorless oil (86 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.46 (m, 1H), 7.38-7.24 (m, 8H), 4.51-4.43 (m, 4H), 3.54 (m, 1H), 3.30 (m, 1H), 3.07 (s, 1.5H), 2.95 (d, 1.5H, J=4.1 Hz), 1.69-1.58 (2m , 2H), 1.40-1.18 (m, 18H), 0.89 (m, 3H)

M^-(LC/MS(ESI)): 493.5; M^+(LC/MS(ESI)): 495.8

HPLC (Condition A), Rt: 6.47 min (HPLC purity: 99.9 %).

Example 8: {(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

Step a) Formation of ethyl {(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate

The same procedure as employed in the preparation of Example 5, step d, but using 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl]amino}methyl)benzoic acid and dodecylmethyl-amine gave the title compound as a colorless oil (56 %).

HPLC (Condition A), Rt: 7.41 min (HPLC purity: 82 %).

Step b) Formation of {(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 5, step e, but using the ethyl {(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate gave the title compound as a colorless oil (68 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.7-7.52 (m, 3H), 7.50-7.30 (m, 5H), 4.62-4.5 (m, 3.5H), 3.85 (m, 0.5H), 3.54 (m, 1H), 3.30 (m, 1H), 3.07 (s, 1.5H), 2.95 (m, 1.5H), 1.72-1.52 (2m, 2H), 1.50-1.10 (m, 18H), 0.95 (m, 3H)

M^-(LC/MS(ESI)): 562.1; M^+(LC/MS(ESI)): 563.8

HPLC (Condition A), Rt: 6.81 min (HPLC purity: 90.5 %).

Example 9: ([1-(tert-butoxycarbonyl)-4-piperidinyl]{4-[(dodecylamino)carbonyl] benzyl}amino)(oxo)acetic acid

Step a) Formation of tert-butyl 4-({4-[(benzyloxy)carbonyl]benzyl}amino)piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 5, step a, but using 1-Boc-4-amino-piperidine gave the title compound as a colorless oil (83 %).

M^+(LC/MS(ESI)): 425.5

HPLC (Condition A), Rt: 3.52 min (HPLC purity: 97.8 %).

Step b) Formation of tert-butyl 4-{{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]-amino}piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 5, step b, but starting from tert-butyl 4-({4-[(benzyloxy)carbonyl]benzyl}amino)piperidine-1-carboxylate gave the title compound as a yellow foam (99 %).

M^-(APCI): 523.4

HPLC (Condition A), Rt: 5.7 min (HPLC purity: 98.4 %).

Step c) Formation of 4-({[1-(tert-butoxycarbonyl)piperidin-4-yl][ethoxy(oxo)acetyl]-amino}methyl)benzoic acid

The same procedure as employed in the preparation of Example 5, step c, but starting from tert-butyl 4-{{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}piperidine-1-carboxylate gave the title compound as a white foam (99 %).

HPLC (Condition A), Rt: 4.1 min (HPLC purity: 95.7 %).

Step d) Formation of tert-butyl 4-{{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)-acetyl]amino}piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 5, step d, but starting from 4-({[1-(tert-butoxycarbonyl)piperidin-4-yl][ethoxy(oxo)acetyl]amino}methyl)benzoic acid gave the title compound as a colorless oil (25 %).

M^-(LC/MS(ESI)): 600.8; M^+(LC/MS(ESI)): 602.5
HPLC (Condition A), Rt: 6.75 min (HPLC purity: 99.1 %).

Step e) Formation of ([1-(tert-butoxycarbonyl)-4-piperidinyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 5, step e, but starting from tert-butyl 4-{{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}piperidine-1-carboxylate gave the title compound as a yellow oil (55 %).
^{1}H NMR (CD_3OD, 300 MHz) δ 7.79(m, 2H), 7.47 (d, 0.5H, J=8.3 Hz), 7.24 (d, 1.5H, J=8.3 Hz), 4.64 (m, 2H), 4.08 (m, 2H), 3.90 (m, 1H), 3.40 (t, 2H, J=7.2 Hz), 2.73 (m, 2H), 1.64 (m, 1H), 1.50(m, 5H), 1.35-1.13 (m, 28H), 0.91 (t, J=7.9 Hz, 3H)
M^-(LC/MS(ESI)): 572.8; M^+(LC/MS(ESI)): 574.5
HPLC (Condition A), Rt: 6.18 min (HPLC purity: 99.2 %).

Example 10: {{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl) benzyl]amino} (oxo)acetic acid

Step a) Formation of the amide of formula (IX) wherein Q is -CONR^{3}R$^{3'}$, e.g. N-dodecyl-4-formyl-benzamide, using isobutyl chloroformate

To a solution of 4-formyl-benzoic acid (22.5 g, 149.9 mmol) and 4-methyl morpholine (18.2 g, 180.0 mmol) in anhydrous THF (200 mL) at -15°C was added dropwise isobutyl chloroformate (22.5 g, 165.0 mmol) under inert atmosphere. After 15 min, dodecylamine (30.56 g, 164.9 mmol) was added at once, and the resulting mixture was stirred 3 h at rt. The solvent was evaporated in vacuum, and the resulting residue dissolved in DCM (200

mL) and washed with a 0.1N aqueous solution of HCl (3x 30), with brine (1x 30 mL). The combined organic layers were dried over MgSO4, filtered and concentrated to afford a white powder (45 g). This crude product was purified by column chromatography over silica gel (EtOAc/c-Hex 4/1 to 1/1 in about 1 h) to give the title compound as a fluffy white solid (38 g, 80 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.06 (s, 1H), 7.76 (m, 4H), 6.18 (m, 1H), 3.44 (q, 2H, J=13 Hz, J=7.2 Hz), 1.61 (m, 2H), 1.4 to 1.2 (m, 18H), 0.86 (t, 3H, J=7.0 Hz)

M^-(LC/MS(ESI)): 316.3; M^+(LC/MS(ESI)): 318.3

HPLC (Condition A), Rt: 5.9 min (HPLC purity: 98.7 %).

Step b) Formation of the secondary amine of formula (III) following the Method G (See Scheme 4), e.g. N-dodecyl-4-[(4-trifluoromethyl-benzylamino)-methyl]-benzamide

To a solution of N-dodecyl-4-formyl-benzamide (3 g, 9.45 mmol) and 4-trifluoromethyl-benzylamine (1.82 g, 10.4 mmol) in DCE (25 mL) was added at once $NaBH(OAc)_3$ (2.80 g, 13.23 mmol) and the resulting mixture was stirred overnight at rt. 5 mL of a saturated aqueous solution of $NaHCO_3$ were added to the reaction mixture, the aqueous layer was separated and washed with DCM (3x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (EtOAc/c-Hex 15/85 to 75/25 in about 1h) to give the title compound as a white solid (2.66 g, 59 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 2H, J=8.3 Hz), 7.61 (d, 2H, 8.1 Hz), 7.49 (d, 2H, J=8.1 Hz), 7.40 (d, 2H, J=8. 2 Hz), 6.12 (br s, 1H), 3.86 (s, 4H), 3.43 (q, 2H, J=13.0 Hz, J=7.0 Hz), 1.63 (m, 2H), 1.6 to 1.2 (br s, 18H), 0.86 (t, 3H, J=7.0 Hz)

M^-(LC/MS(ESI)): 475.32; M^+(LC/MS(ESI)): 477.4

HPLC (Condition A), Rt: 4.97 min (HPLC purity: 95.1 %).

Step c) Formation of the oxamic ester of formula (II-1) following the Method A (See Scheme 1), e.g. ethyl {{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]-amino}-(oxo)acetate

To a solution of N-dodecyl-4-[(4-trifluoromethyl-benzylamino)-methyl]-benzamide (2.60 g, 5.46 mmol) and TEA (1.104 g, 10.91 mmol) in anhydrous THF (20 mL) at 0°C under inert atmosphere, was added dropwise the chloro-oxo-acetic acid ethyl ester (1.117 g, 8.18 mmol). The reaction mixture was stirred at 0°C for 1.25 h. The solvents were evaporated and 50 mL of DCM were added. 20 mL of H_2O were added to the reaction mixture, the aqueous layer was separated and extracted with DCM (3x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/3 to 1/2 on about 1h) to give the title compound as a yellow solid (2.770 g, 88 %).

^{1}H NMR (CDCl3, 300 MHz) δ 7.73 (m, 2H), 7.60 (m, 2H), 7.37-7.23 (m, 4H), 6.09 (br s, 1H), 4.5 (s, 2H), 4.37-4.32 (m, 4H), 3.43 (m, 2H), 1.60 (m, 2H), 1.36-1.20 (m, 21H), 0.86 (m, 3H)

M^-(LC/MS(ESI)): 575.5; M^+(LC/MS(ESI)): 577.4

HPLC (Condition A), Rt: 6.84 min (HPLC purity: 99.2 %).

Step d) Formation of the oxamic acid of formula (I), e.g. {{4-(dodecylamino)carbonyl]-benzyl} [4-(trifluoromethyl) benzyl]amino} (oxo)acetic acid

The same procedure as employed in the preparation of Example 1, step e, but starting from ethyl {{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetate gave the title compound as awhite powder (83 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.79 (m, 2H), 7.65 (m, 2H), 7.51 (d, 1H,J=8.1 Hz), 7.41 (m, 2H), 7.30 (d, 1H, J=8.1 Hz), 4.6 (m, 4H), 3.33 (t, 2H, J=7.1 Hz), 1.62 (m, 2H), 1.37-1.31 (m, 18H), 0.88 (t, 3H, J=6.5 Hz)

M^-(LC/MS(ESI)): 547.3; M^+(LC/MS(ESI)): 549.5

HPLC (Condition A), Rt: 6.34 min (HPLC purity: 99.2 %).

Analysis calculated for $C_{30}H_{39}F_3N_2O_4$: C, 65.68; H, 7.16 ; N, 5.11 %. Found: C, 65.65; H, 7.18 ; N, 5.08 %

Example 11: {{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino} (oxo)acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt

The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine and {{4-(dodecylamino)carbonyl]benzyl} [4-(trifluoromethyl) benzyl]amino} (oxo)acetic acid gave the title compound as a white powder (81 %).
M^-(LC/MS(ESI)): 548.1; M^+(LC/MS(ESI)): 550.2
HPLC (Condition A), Rt: 6.3 min (HPLC purity: 99 %).
Analysis calculated for $C_{30}H_{39}F_3N_2O_4.C_7H_{17}NO_5 \cdot 1.1\ H_2O$: C, 58.19; H, 7.39 ; N, 5.50 %. Found: C, 58.09; H, 7.66; N, 5.45 %

Example 12: {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl] amino}-(oxo)acetic acid

Step a) Formation of N-dodecyl-4-({[3-(trifluoromethyl)benzyl]amino}methyl)benzamide

The same procedure as employed in the preparation of Example 10, step b, but starting from 3-trifluoromethyl-benzylamine gave the title compound as a colorless oil (55 %).
^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.38 (t, 1H, J=5.5 Hz), 7.78 (d, 2H, J=8.2 Hz), 7.71 (s, 1H), 7.65-7.51 (m, 3H), 7.41 (d, 2H, J=8.1 Hz), 3.75 (s, 2H), 3.72 (s, 2H), 3.38-3.28 (m, 2H), 1.50 (m, 2H), 1.23 (br s, 18H), 0.84 (t, 3H, J=8.0 Hz)
M^+(LC/MS(ESI)): 477.5
HPLC (Condition A), Rt: 4.90 min (HPLC purity: 95.3 %).

Step b) Formation of ethyl {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)-benzyl]amino}(oxo)acetate

The same procedure as employed in the preparation of Example 10, step c, but starting from N-dodecyl-4-({[3-(trifluoromethyl)benzyl]amino}methyl)benzamide gave the title compound as a colorless oil (97 %).

M^+(LC/MS(ESI)): 577.6

HPLC (Condition A), Rt: 6.98 min (HPLC purity: 97.4 %).

Step c) Formation of {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 10, step d, but starting from ethyl {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetate gave the title compound as a colorless oil (82 %).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.85-7.55 (m, 6H), 7.35 (d, 1H, J=8.2 Hz), 7.23 (d, 1H, J=8.2 Hz), 4.55 (d, J=6.0 Hz, 2H), 4.50 (d, J=12.4 Hz, 2H), 3.22 (t, J=7.4 Hz, 2H), 1.58-1.39 (m, 2H), 1.37-1.11 (m, 18H), 0.85 (t, J=6.7 Hz, 3H)

M^-(LC/MS(ESI)): 547.4; M^+(LC/MS(ESI)): 549.4

HPLC (Condition A), Rt: 6.69 min (HPLC purity: 97.9 %).

Example 13: {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl] amino}-(oxo)acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt

The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine and {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl] amino}(oxo)acetic acid gave the title compound as a white fluffy powder (82 %).

M^-(LC/MS(ESI)): 547.4; M^+(LC/MS(ESI)): 549.4

HPLC (Condition A), Rt: 6.69 min (HPLC purity: 99.1 %).

Analysis calculated for $C_{30}H_{39}F_3N_2O_4.C_7H_{17}NO_5$: C 59.74; H 7.59; N 5.65 %. Found: C 59.13; H 7.90; N 5.57 %

Example 14: ({[1-(tert-butoxycarbonyl)-4-piperidinyl]methyl}{4-[(dodecylamino) carbonyl]benzyl}amino)(oxo)acetic acid

Step a) Formation of tert-butyl 4-[({4-[(dodecylamino)carbonyl]benzyl}amino)methyl]-piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 10, step b, but starting from 4-(aminomethyl)-1-N-Boc-piperidine gave the title compound as a colorless oil (31 %).

M^-(ESI): 514.2

HPLC (Condition B), Rt: 6.2 min (HPLC purity: 96.2 %).

Step b) Formation of tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)-acetyl]amino}methyl)piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 10, step c, but starting from tert-butyl 4-[({4-[(dodecylamino)carbonyl]benzyl}amino)methyl]piperidine-1-carboxylate gave the title compound as a colorless oil (81 %).

^{1}H NMR (CDCl3, 300 MHz) δ 7.75 (m, 2H), 7.30 (m, 2H), 6.25 (br s, 1H), 4.49-4.30 (m, 2H), 4.40-4.20 (m, 2H), 4.05 (br s, 2H), 3.42 (m, 2H), 3.20-3.05 (m, 2H), 2.60 (m, 2H), 1.9-1.7 (m, 1H), 1.55 (m, 4H), 1.40-1.0 (m, 31H), 0.86 (m, 3H)

M^-(APCI): 614.2; M^+(APCI): 616.4

HPLC (Condition B), Rt: 8.8 min (HPLC purity: 97.8 %).

Step c) Formation of ({[1-(tert-butoxycarbonyl)-4-piperidinyl]methyl}{4-[(dodecylamino) carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 10, step d, but starting from tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}-methyl)piperidine-1-carboxylate gave the title compound as a colorless oil (97 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (m, 2H), 7.26 (m, 2H), 6.21(m, 1H), 4.84 (br s, 1H), 4.69 (br s, 1H), 4.10 (m, 2H), 3.45 (m, 3H), 3.20 (m, 1H), 2.63 (m, 2H), 1.85 (m, 1H), 1.61 (m, 4H), 1.45-1.05 (m, 30H), 0.88 (t, J=8.0 Hz, 3H)
M^-(APCI): 586.2
HPLC (Condition A), Rt: 8.15 min (HPLC purity: 91.6 %).

Example 15: oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetic acid

Step a) Formation of the secondary amine of formula (III) following the Method J (See Scheme 4), e.g. tert-butyl 4-({[4-(trifluoromethyl)benzyl]amino}methyl)phenylcarbamate
To a solution of 4-(aminomethyl)-1-N-Boc-aniline (1.778 g, 8.0 mmol) and 4-trifluoromethyl-benzaldehyde (1.156 g, 6.64 mmol) in DCE (50 mL) was added at once $NaBH(OAc)_3$ (2.374 g, 11.20 mmol) and the resulting mixture was stirred overnight at rt. 15 mL of a saturated aqueous solution of $NaHCO_3$ were added to the reaction mixture, the aqueous layer was separated and washed with DCM (3x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/1 then 7/3) to give the title compound as a colorless oil (2.688 g, 88 %).
^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.3 (s, 1H), 7.66 (d, 2H, J=8.0 Hz), 7.56 (d, 2H, J=8.0 Hz), 7.37 (d, 2H, J=8.5 Hz), 7.20 (d, 2H, J=8.5 Hz), 3.73 (s, 2H), 3.59 (s, 2H), 1.47 (s, 9H)
M^-(LC/MS(ESI)): 379.2; M^+(LC/MS(ESI)): 381.4
HPLC (Condition A), Rt: 3.38 min (HPLC purity: 99.1 %).

Step b) Formation of the oxamic ester of formula (II-2) following the Method C (See Scheme 2), e.g. ethyl {{4-[(tert-butoxycarbonyl)amino]benzyl}[4-(trifluoromethyl-)benzyl]amino}-(oxo)acetate

To a solution tert-butyl 4-({[4-(trifluoromethyl)benzyl]amino}methyl)phenylcarbamate (2.69 g, 7.07 mmol) and DIEA (1.83 g, 14.13 mmol) in anhydrous DCM (30 mL) at 0°C under inert atmosphere, was added dropwise the chloro-oxo-acetic acid ethyl ester (1.06 g, 7.77 mmol). The reaction mixture was stirred 3h at 0°C, then 1 h at rt. A 1 N aqueous solution of HCl (5 mL) was added and the mixture was extracted with DCM (3x 30 mL). The combined organic layers were washed with water (3x 20 mL), dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4) to give the title compound as a colorless oil (2.980 g, 88 %).

M^-(LC/MS(ESI)): 479.3

HPLC (Condition A), Rt: 5.65 min (HPLC purity: 99.9 %).

Step c) Deprotection of the oxamic ester of formula (II-2) (See Scheme 2), formation of e.g. ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate

To a solution of ethyl {{4-[(tert-butoxycarbonyl)amino]benzyl}[4-(trifluoromethyl)-benzyl]amino}(oxo)acetate (2.980 g, 6.2 mmol) in DCM (40 mL) was added TFA (10 mL) and the resulting reaction mixture was stirred for 4 h at rt. The solvents were evaporated under vacuum to afford an orange oil. This crude product was dissolved in Et_2O, washed with a saturated aqueous solution of $NaHCO_3$, water (2x 20 mL) and brine (1x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a orange oil (2.245 g, 95 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 7.59 (m, 2H), 7.33 (m, 2H), 7.01 (m, 2H), 6.65 (m, 2H), 4.49 (s, 1H), 4.40-4.28 (m, 4H), 4.20 (s, 1H), 1.38-1.26 (m, 3H)

M^-(LC/MS(ESI)): 379.1

HPLC (Condition A), Rt: 3.3 min (HPLC purity: 92.4 %).

Step d) Formation of the oxamic ester of formula (I-2) following the Method C (See Scheme 2), e.g. ethyl oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetate

To a cold (0°C) solution of ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl] amino}-(oxo)acetate (800 mg, 2.10 mmol) and DIEA (326 mg, 2.52 mmol) in DCM (10.0 mL) was added tridecanoyl chloride (539 mg, 2.31 mmol) under inert atmosphere. The resulting reaction mixture was stirred 1 h at 0°C then 3.5 h at rt. A 1 N aqueous solution of HCl (2 mL) was added and the mixture was extracted with DCM (3x 30 mL). The combined organic layers were washed with water (3x 20 mL), dried over $MgSO_4$, filtered and concentrated to afford a colorless oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4) to give the title compound as a colorless oil (1.067 g, 88 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 7.59 (m, 2H), 7.50 (m, 2H), 7.38 (d, 2H, J=8.1 Hz), 7.29 (d, 2H, J=8.0 Hz), 7.18 (m, 2H), 4.47 (m, 2H), 4.37-4.28 (m, 4H), 2.34 (t, 2H, J=7.5 Hz), 1.71 (m, 2H), 1.38-1.26 (m, 21H), 0.87 (t, J=8.1 Hz, 3H)
M^-(LC/MS(ESI)): 575.2; M^+(LC/MS(ESI)): 577.0
HPLC (Condition A), Rt: 7.1 min (HPLC purity: 98.2 %).

Step e) Formation of the oxamic ester of formula (I-2), e.g. oxo{[4-(tridecanoylamino)-benzyl][4-(trifluoromethyl)benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 1, step e, but starting from ethyl oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetate gave the title compound as awhite powder (99 %).
^1H NMR (CD_3OD, 300 MHz) δ 7.65-7.12 (m, 8H), 4.54 (s, 2H), 4.45 (s, 2H), 2.34 (t, J=6.9 Hz, 2H), 1.69-1.63 (m, 2H), 1.40-1.22 (m, 18H), 0.87 (t, J=8.6 Hz, 3H)
M^-(LC/MS(ESI)): 547.5; M^+(LC/MS(ESI)): 549.3
HPLC (Condition A), Rt: 6.56 min (HPLC purity: 99.6 %).
Analysis calculated for $C_{30}H_{39}F_3N_2O_4.C_7H_{17}NO_5$: C, 59.74; H, 7.59; N, 5.65 %. Found: C, 59.54; H, 7.68; N, 5.53 %

Example 16: oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt

The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine and oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl) benzyl]amino}acetic acid gave the title compound as a white powder (83 %).

M^-(LC/MS(ESI)): 547.5; M^+(LC/MS(ESI)): 549.3

HPLC (Condition A), Rt: 6.56 min (HPLC purity: 99.6 %).

Analysis calculated for $C_{30}H_{39}F_3N_2O_4.C_7H_{17}NO_5$: C, 59.74; H, 7.59; N, 5.65 %. Found: C, 59.54; H, 7.68; N, 5.53 %

Example 17: [benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetic acid

Step a) Formation of tert-butyl 4-[(benzylamino)methyl]phenylcarbamate

The same procedure as employed in the preparation of Example 15, step a but using 4-(aminomethyl)-1-N-Boc-aniline and benzaldehyde gave the title compound as a white solid (61 %).

M^+(ESI): 313.2

HPLC (Condition A), Rt: 2.89 min (HPLC purity: 99.4 %).

Step b) Formation of ethyl (benzyl{4-[(tert-butoxycarbonyl)amino]benzyl}amino)(oxo)-acetate

The same procedure as employed in the preparation of Example 15, step b but using tert-butyl 4-[(benzylamino)methyl]phenylcarbamate gave the title compound as a brown foam (89 %).

M^-(APCI): 411.0; M^+(APCI): 413.2

HPLC (Condition A), Rt: 5.32 min (HPLC purity: 98.1 %).

Step c) Formation of ethyl [(4-aminobenzyl)(benzyl)amino](oxo)acetate

The same procedure as employed in the preparation of Example 15, step c but using ethyl (benzyl{4-[(tert-butoxycarbonyl)amino]benzyl}amino)(oxo)acetate gave the title compound as a brown oil (99.9 %).

HPLC (Condition A), Rt: 2.69 min (HPLC purity: 91.5 %).

Step d) Formation of ethyl [benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino]-(oxo)acetate

The same procedure as employed in the preparation of Example 15, step d but using 4-hexyloxy-benzoyl chloride and ethyl [(4-aminobenzyl)(benzyl)amino](oxo)acetate gave the title compound as a colorless oil (58 %).

M^-(ESI): 515.2

HPLC (Condition A), Rt: 6.0 min (HPLC purity: 94.9 %).

Step e) Formation of [benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 15, step e using ethyl [benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetate gave the title compound as a white gum (99.9 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.93 (d, 2H, J=8.3 Hz), 7.67 (m, 2H), 7.38-7.25 (m, 7H), 7.02 (d, 2H, J=9.0 Hz), 4.43 (m, 4H), 4.06 (t, 2H, J=6.4 Hz), 1.81 (m, 2H), 1.50 (m, 2H), 1.38 (m, 4H), 0.88 (t, J=7.9 Hz, 3H)

M^-(LC/MS(ESI)): 487.4; M^+(LC/MS(ESI)): 489.4

HPLC (Condition A), Rt: 5.42 min (HPLC purity: 96.4 %).

Example 18: oxo{[4-(trifluoromethyl)benzyl][4-(10-undecenoylamino) benzyl]amino}-acetic acid

Step a) Formation of ethyl oxo{[4-(trifluoromethyl)benzyl][4-(undec-10-enoylamino)-benzyl]amino}acetate

The same procedure as employed in the preparation of Example 15, step d using ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate and undec-10-enoyl chloride gave the title compound as a colorless oil (71 %).

HPLC (Condition A), Rt: 6.7 min (HPLC purity: 99 %).

Step b) Formation of oxo{[4-(trifluoromethyl)benzyl][4-(10-undecenoylamino)benzyl] amino}acetic acid

The same procedure as employed in the preparation of Example 15, step e using ethyl oxo{[4-(trifluoromethyl)benzyl][4-(undec-10-enoylamino)benzyl]amino}acetate gave the title compound as a colorless oil (89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.2 (s, 1H), 8.03 (d, 1H, J=8.0 Hz), 7.61-7.51 (m, 3H), 7.50-7.44 (t, 1H, J=9.0 Hz), 7.38 (d, 1H, J=7.9 Hz), 7.29 (d, 1H, J=7.1 Hz), 7.17 (d, 1H, J=7.7 Hz), 7.11 (d, 1H, J=7.7 Hz), 5.84-5.75 (m, 1H), 5.02-4.91 (m, 2H), 4.58-4.44 (m, 4H), 2.38 (m, 2H), 2.06 (m, 2H), 1.7 (br s, 2H), 1.29 (br s, 10H)

M^-(LG/MS(ESI)): 516.9; M^+(LC/MS(ESI)): 519.2

HPLC (Condition A), Rt: 5.7 min (HPLC purity: 99.4 %).

Example 19: oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)benzyl] amino}acetic acid

Step a) Formation of ethyl oxo{{4-[(9E)-tetradec-9-enoylamino]benzyl}[4-(trifluoro-methyl)benzyl]amino}acetate

The same procedure as employed in the preparation of Example 15, step d using ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate and tetradec-9-enoyl chloride gave the title compound as a colorless oil (81 %).

M^-(LC/MS(ESI)): 588.0

HPLC (Condition A), Rt: 7.3 min (HPLC purity: 96.9 %).

Step b) Formation of oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)-benzyl] amino}acetic acid

The same procedure as employed in the preparation of Example 15, step e using ethyl oxo{{4-[(9E)-tetradec-9-enoylamino]benzyl}[4-(trifluoromethyl)benzyl]amino}acetate gave the title compound as a colorless oil (94 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.58-7.00 (m, 8H), 5.30-5.19 (m, 2H), 4.45 (s, 2H), 4.37 (s, 2H), 2.26 (t, 2H, J=7.3 Hz), 1.98-1.88 (m, 4H), 1.66-1.53 (m, 2H), 1.32-1.16 (m, 12H), 0.80 (t, 3H)

M^-(LC/MS(ESI)): 559.7; M^+(LC/MS(ESI)): 561.2

HPLC (Condition A), Rt: 6.72 min (HPLC purity: 98.9 %).

Example 20: oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)benzyl]-amino}acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt

The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine and oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)benzyl] amino}acetic acid gave the title compound as a white fluffy powder (93.8 %).

M^-(LC/MS(ESI)): 559.7; M^+(LC/MS(ESI)): 561.2

HPLC (Condition A), Rt: 6.72 min (HPLC purity: 98.9 %).

Analysis calculated for $C_{31}H_{39}F_3N_2O_4.C_7H_{17}NO_5$: C, 60.38; H, 7.47; N, 5.56 %. Found: C, 60.19; H, 7.70; N, 5.36 %

Example 21: {benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetic acid

Step a) Formation of ethyl {benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetate

The same procedure as employed in the preparation of Example 5, step d using ethyl [(4-aminobenzyl)(benzyl)amino](oxo)acetate and tridecanoic acid gave the title compound as a colorless oil (39 %).

M⁻(ESI): 507.2

HPLC (Condition A), Rt: 7 min (HPLC purity: 91.3 %).

Step b) Formation of oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)-benzyl] amino}acetic acid

The same procedure as employed in the preparation of Example 15, step e using ethyl {benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetate gave the title compound as a white gum (99 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.54 (m, 2H), 7.38-7.15 (m, 7H), 4.43 (m, 4H), 2.38 (t, 2H, J=7.3 Hz), 1.69 (m, 2H), 1.27 (m, 18H), 0.90 (t, J=8.0 Hz, 3H)

M⁻(ESI): 479.2

HPLC (Condition A), Rt: 6.19 min (HPLC purity: 94.9 %).

Example 22: {{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl] amino}(oxo)acetic acid

Step a) Formation of ethyl {{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)-benzyl]amino}(oxo)acetate

To a solution of ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate (38 mg, 0.10 mmol) and 1,2-dodecylene oxide (22 mg, 0.12 mmol) in 1.0 mL CH_3CN were added at once magnesium perchlorate (27 mg, 0.12 mmol) under inert atmosphere. The reaction mixture was stirred 24 at rt. 2 mL of H_2O were added and the resulting mixture

was extracted with EtOAc (2x 5mL), dried over $MgSO_4$, filtered and the solvents were evaporated under vacuum to give a slightly yellow oil (61 mg).
Purification on SiO_2 (AcOEt/c-Hex) gave the title compound as a colorless oil (15.3 mg, 27 %)

^1H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.46 (m, 2H), 7.36-7.21 (m, 2H), 7.05-6.88 (m, 2H), 6.61-6.47 (m, 2H), 4.43 (s, 1H), 4.38-4.17 (m, 4H), 4.14 (s, 1H), 3.17 (br s, 1H), 3.25-3.13 (m, 1H), 3.01-2.81 (m, 1H), 1.55-1.05 (m, 23H), 0.81 (t, J=7.9 Hz, 3H)
M^+(LC/MS(ESI)): 565.4
HPLC (Condition A), Rt: 5.96 min (HPLC purity: 94.8 %).

Step b) Formation of {{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 1, step e using ethyl {{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetate gave the title compound as a yellow solid (90 %).
^1H NMR (CD_3OD, 300 MHz) δ 7.57 (m, 2H), 7.46 (m, 1H), 7.33 (m, 1H), 7.18 (d, 1H, J=7.5 Hz), 7.10 (d, 1H, J=7.2 Hz), 6.83 (m, 2H), 4.69 (b rs, 1H), 4.48 (br s, 2H), 4.38 (s, 1H), 3.72 (br s, 1H), 3.25-3.15 (m, 1H), 3.13-2.98 (m, 1H), 1.47 (br s, 2H), 1.26 (br s, 16H), 0.86 (br s, 3H)
M^-(LC/MS(ESI)): 535.0; M^+(LC/MS(ESI)): 537.1
HPLC (Condition A), Rt: 5.11 min (HPLC purity: 88.5 %).

Example 23: oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]amino}acetic acid

Step a) Formation of N-hydroxydodecanimidamide
To a solution of undecyl cyanide (1.810 g, 9.98 mmol) in EtOH (20 mL) was added a 50 % aqueous solution of hydroxylamine (1 mL) and the resulting reaction mixture was stirred at

70°C for 48h. The solvents were evaporated and the resulting white solid was dissolved in EtOAc (100 mL) and washed with H_2O (2x 20mL), dried over MgSO4, filtered and the solvents evaporated under vacuum to give the title compound as a white solid (2.001g, 94 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21-4.99 (br s, 1H), 4.49 (br s, 2 H), 2.07 (t, J=7.6 Hz, 2H), 1.55-1.40 (m, 2H), 1.34-1.09 (m, 16H), 0.81 (t, J=7.0 Hz, 3H)

Step b) Formation of benzyl 4-({(tert-butoxycarbonyl)[4-(trifluoromethyl)benzyl]-amino}methyl)benzoate

To a solution of benzyl 4-({[4-(trifluoromethyl)benzyl] amino}methyl)benzoate (3.60 g, 9.01 mmol) and triethylamine (1.094 g, 10.82 mmol) in DCM (50 mL) was added the di-tert-butyl dicarbonate (2.164 g, 9.91 mmol) and the resulting reaction mixture was stirred at rt for 5 h. H_2O was added (10 mL) and the mixture extracted with DCM (3x 50 mL). The combined organic layers were washed with with a 1 N aqueous solution of HCl (10 mL), a saturated aqueous solution of $NaHCO_3$, water (2x 20 mL) and brine (1x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a colorless oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 5/95) to give the title compound as a colorless oil (4.303 g, 96 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J=8.1 Hz, 2H), 7.67 (d, J=8.1 Hz, 2H), 7.60-7.22 (m, 9H), 5.46 (s, 2H), 4.57 (s, 2H), 4.58 (s, 2H), 1.56 (s, 9H)

HPLC (Condition A), Rt: 6.55 min (HPLC purity: 99.7 %).

Step c) Formation of 4-({(tert-butoxycarbonyl)[4-(trifluoromethyl)benzyl]amino}methyl)-benzoic acid

H_2 (1 atm) was bubbled slowly trough a suspension of 10 % Pd/C (917 mg) in EtOH (25 mL) for 15 min at rt. To this suspension was then added a solution of benzyl 4-({(tert-butoxycarbonyl)[4-(trifluoromethyl)benzyl]amino}methyl)benzoate (4.303 g, 8.61 mmol) diluted in EtOH (5 mL). The resulting reaction mixture was stirred under 1 atm H_2 for 4.5 h

at rt. The reaction mixture was filtered over a pad of celite to remove the catalyst. EtOH was evaporated to afford the title compound as a colorless oil used in the next steps without further purification (3.520 g, 99 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J=8.1 Hz, 2H), 7.62 (d, J=8.1 Hz, 2H), 7.45-7.21 (m, 4H), 5.54 (s, 2H), 4.45 (s, 2H), 1.50 (s, 9H)

HPLC (Condition A), Rt: 5.42 min (HPLC purity: 96.1 %).

Step d) Formation of tert-butyl 4-{[(dodecanimidoylamino)oxy]carbonyl}benzyl[4-(trifluoromethyl)benzyl]carbamate

To a solution of 4-({(tert-butoxycarbonyl)[4-(trifluoromethyl)benzyl]amino}methyl)-benzoic acid (102 mg, 0.25 mmol), N-hydroxydodecanimidamide (70 mg, 0.33 mmol) and DMAP (3 mg, 0.03 mmol) in anhydrous DCM (15 mL) was added EDC (62 mg, 0.33 mmol) and the resulting reaction mixture was stirred at RT for 14 h. Evaporation of the solvents gave an oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 80/20) to give the title compound as a colorless oil (36 mg, 24 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, J=8.1 Hz, 2H), 7.60 (d, J=8.1 Hz, 2H), 7.40-7.20 (m, 4H), 4.88 (br s, 2H), 4.51 (s, 2H), 4.42(s, 2H), 2.36 (t, J=8.2 Hz, 2H), 1.75-1.59(m, 2H), 1.49 (s, 9H), 1.45-1.16 (m, 16H), 0.89 (t, J=7.0 Hz, 3H)

HPLC (Condition A), Rt: 5.42 min (HPLC purity: 96.1 %).

Step e) Formation of tert-butyl 4-(trifluoromethyl)benzyl[4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]carbamate

A solution of tert-butyl 4-{[(dodecanimidoylamino)oxy]carbonyl}benzyl[4-(trifluoromethyl)benzyl]carbamate in pyridine was stirred under inert atmosphere at 120°C for 4 h. The resulting brown solution was evaporated (under high vacuum) and the resulting oil was purified by column chromatography over silica gel (AcOEt/c-Hex 20/80) to give the title compound as a colorless oil (50 mg, 71 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (d, J=8.1 Hz, 2H), 7.51 (d, J=8.1 Hz, 2H), 7.35-7.14 (m, 4H), 4.43 (s, 2H), 4.35 (s, 2H), 2.71 (t, J=7.5 Hz, 2H), 1.80-1.65 (m, 2H), 1.41 (s, 9H), 1.36-1.12 (m, 16H), 0.89 (t, J=7.0 Hz, 3H)

Step f) Formation of N-[4-(trifluoromethyl)benzyl]-N-[4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]amine hydrochloride

To a cold (0°C) solution of tert-butyl 4-(trifluoromethyl)benzyl[4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]carbamate (43 mg, 0.07 mmol) in DCM (3 mL) was added a solution of HCl (4N in dioxane, 3 mL) and the resulting reaction mixture was stirred 3h at 0°C, then 14h at rt. Evaporation of the solvent gave the title compound as a white powder used in the next steps without further purification (29 mg, 99 %).

M^-(APCI): 486.0; M^+(APCI): 488.2

HPLC (Condition A), Rt: 5.4 min (HPLC purity: 82 %).

Step g) Formation of ethyl oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]amino}acetate

To a cold (0°C) solution of *N-[4-(trifluoromethyl)benzyl]-N-[4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]amine hydrochloride* (45 mg, 0.09 mmol) and DIEA (24 mg, 0.19 mmol) in anhydrous DCM (1 mL) was added dropwise the chloro-oxo-acetic acid ethyl ester (24 mg, 0.19 mmol). The reaction mixture was stirred at 0°C for 3 h. Evaporation of the solvents under vacuum gave an orange oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/9) to give the title compound as a colorless oil (38 mg, 75 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J=8.3 Hz, 1H), 8.02 (d, J=8.3 Hz, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.53 (d, J=8.2 Hz, 1H), 7.39-7.21 (m, 4H), 4.50 (s, 2H), 4.37 (s, 2H), 4.29 (dq, J1=7.1 Hz, J2=2.3 Hz, 2H), 2.72 (t, J=7.4 Hz, 2H), 1.85-1.65 (m, 2H), 1.41-1.05 (m, 19H), 0.89 (t, J=7.0 Hz, 3H)

HPLC (Condition A), Rt: 7.5 min (HPLC purity: 88.8 %).

Step h) Formation of oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 1, step e using ethyl oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]amino}acetate gave the title compound as a white powder (89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10-7.99 (m, 2H), 7.61-7.50 (m, 2H), 7.32 (d, J=8.6 Hz, 2H), 7.27 (d, J=7.9 Hz, 2H), 4.98 (s, 2H), 4.58 (s, 2H), 2.74 (t, J=8.0 Hz, 2H), 1.81-1.66 (m, 2H), 1.42-1.04 (m, 16H), 0.81 (t, J=6.7 Hz, 3H)
M$^-$(APCI): 558.4
HPLC (Condition A), Rt: 7.4 min (HPLC purity: 98.6 %).

Example 24: {({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

Step a) Formation of 2-(thien-2-ylmethyl)-1H-isoindole-1,3(2H)-dione

A solution of thiophene-2-methylamine (4.203 g, 37.13 mmol) and of phtalic anhydride (5.00 g, 33.76 mmol) in toluene (100 mL) was stirred and heated at reflux for 3 h to remove the formed water by azeotropic distillation (Dean-Stark). The solvent was then evaporated under vacuum. The residue was dissolved in DCM (100 mL), washed with water (3x 30 mL), dried over $MgSO_4$, filtered and concentrated to afford the title compound as a white solid (7.78 g, 95 %).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, 1H. J=5.4 Hz), 7.83 (d, 1H. J=5.4 Hz), 7.69 (d, 1H, J=5.4 Hz), 7.68 (d, 1H, J=5.4 Hz), 7.20 (d, 0.5H, J=5.2 Hz), 7.19 (d, 0.5H, J=5.2 Hz), 7.14 (m, 1H), 6.92 (d, 0.5H, J=5.1 Hz), 6.91 (d, 0.5H, J=5.1 Hz), 5.01 (s, 2H)
HPLC (Condition A), Rt: 4.11 min (HPLC purity: 99.2 %).

Step b) Formation of 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]thiophene-2-sulfonyl chloride

To a cold (-78°C) solution of 2-(thien-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (6.78 g, 27.87 mmol) in DCM (56 mL) was added dropwise (in about 10 min) chlorosulfonic acid (16.237 g, 139.3 mmol, 9.33 mL, d: 1.74) diluted in DCM (9.3 mL). The reaction mixture was stirred 2 h at –78°C, then 1 h at –40°C and overnight at rt. The resulting brown solution was poured on ice. The mixture was extracted with DCM (3x 200 mL), and the combined organic layers were washed with water (3x 200 mL), dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4 to 1/3 to 1/2 in about 1 h) to give the title compound as a white solid (6.42 g, 67 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, 1H. J=5.5 Hz), 7.87 (d, 1H. J=5.5 Hz), 7.76 (d, 1H, J=5.5 Hz), 7.75 (d, 1H, J=5.5 Hz), 7.71 (d, 1H, J=4.0 Hz), 7.18 (d, 1H, J=4.0 Hz), 5.05 (s, 2H)

HPLC (Condition A), Rt: 4.6 min (HPLC purity: 94.8 %).

Step c) Formation of 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-N-dodecylthiophene-2-sulfonamide

To a solution of 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]thiophene-2-sulfonyl chloride (2.00 g, 5.85 mmol), DIEA (1.134 g, 8.78 mmol) in DCM (20 mL) was added dodecyl amine (1.41 g, 7.61 mmol) at rt and the reaction mixture was stirred for 2 h at rt. A 1 M aqueous solution of HCl (10 mL) was added and the aqueous layers were extracted with DCM (2x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4 to 4/1 in about 0.5 h) to give the title compound as a white solid (2.10 g, 73 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.91 (m, 2H), 7.85 (m, 2H), 7.43 (d, 1H, J=3.7 Hz), 7.17 (d, 1H, J=3.7 Hz), 5.05 (s, 2H), 2.90 (t, 2H, J=6.9 Hz), 1.50-1.38 (m, 2H), 1.35-1.16 (m, 18H), 0.86 (t, J=7.9 Hz, 3H)

M^-(LC/MS): 489.3; M^+(LC/MS): 491.2

HPLC (Condition A), Rt: 6.64 min (HPLC purity: 95.9 %).

Step d) Deprotection of 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-N-dodecylthiophene-2-sulfonamide; formation of 5-(aminomethyl)-N-dodecylthiophene-2-sulfonamide

To a solution of 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-N-dodecylthiophene-2-sulfonamide (2.069 g, 4.22 mmol) in EtOH (20 mL) was added hydrazine hydrate (0.614 mL, 633 mg, d: 1.030, 12.65 mmol). The resulting reaction mixture was stirred at reflux for 3h and then cooled down to rt. The white precipitate was removed by filtration and the solvents were evaporated under vacuum. The residue was dissolved in DCM (20mL) and the precipitate removed by filtation. The collected solvents were concentrated to afford of a colorless oil which turns solid on standing (1.5 g, 99 %).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.37 (m, 1H), 6.94 (m, 1H), 3.91 (s, 2H), 2.78 (m, 2H), 1.95-1.65 (m, 20H), 0.86 (t, J=7.6 Hz, 3H)

M^-(LC/MS (ESI)): 359.2; M^+(LC/MS (ESI)): 361.2

HPLC (Condition A), Rt: 4.5 min (HPLC purity: 95 %).

Step e) Formation of N-dodecyl-5-({[4-(trifluoromethyl)benzyl]amino}methyl)thiophene-2-sulfonamide

To a solution of 5-(aminomethyl)-N-dodecylthiophene-2-sulfonamide (797 mg, 2.21 mmol) and 4-trifluoromethyl-benzaldehyde (350 mg, 2.01 mmol) in DCE (50 mL) was added at once $NaBH(OAc)_3$ (596 mg, 2.81 mmol) and the resulting mixture was stirred overnight at rt. 30 mL of a saturated aqueous solution of $NaHCO_3$ were added to the reaction mixture, the aqueous layer was separated and washed with DCM (3x 200 mL). The combined

organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellowish oil. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4 to 1/2 in about 1h) to give the title compound as a colorless oil (675 mg, 64 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (m, 2H), 7.46 (m, 2H), 7.37 (d, 0.7H, J=8.0 Hz), 6.88 (d, 1H, J=3.8 Hz), 4.00 (s, 2H), 3.90 (s, 2H), 3.02 (m, 2H), 1.85-1.55 (m, 2H), 1.5 (m, 2H), 1.22 (s, 18H), 0.87 (t, 3H, 6.6 Hz)
M^-(LC/MS (ESI)): 517.2; M^+(LC/MS (ESI)): 519.2
HPLC (Condition A), Rt: 5.27 min (HPLC purity: 97.2 %).

Step f) Formation of ethyl {({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate

The same procedure as employed in the preparation of Example 1, step b but using N-dodecyl-5-({[4-(trifluoromethyl)benzyl]amino}methyl)thiophene-2-sulfonamide gave the title compound as a colorless oil (360 g, 45 %).
^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (t, 2H, J=9.0 Hz), 7.42 (m, 2H), 7.37 (d, 0.7H, J=8.0 Hz), 6.87 (d, 0.3H, J=3.8 Hz), 6.86 (d, 0.7H, J=3.8 Hz), 4.60 (m, 2H), 4.52 (m, 2H), 4.36 (m, 2H), 3.02 (m, 2H), 1.50 (m, 3H), 1.40-1.20 (m, 21H), 0.86 (t, 3H, 6.6 Hz)
M^-(APCI): 617.2; M^+(APCI): 619.2
HPLC (Condition A), Rt: 7.1 min (HPLC purity: 99.9 %).

Step g) Formation of {({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 1, step e but using ethyl {({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)[4-(trifluoromethyl)benzyl]amino}(oxo)-acetate gave the title compound as a colorless foam (96 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.61 (m, 2H), 7.52 (m, 1H), 7.40 (m, 1H), 7.32 (m, 1H), 7.08 (m, 0.5H), 6.85 (m, 0.5H), 4.71 (m, 4H), 2.88 (m, 2H), 1.46 (m, 2H), 1.27 (m, 18H), 0.87 (t, J=8.1 Hz, 3H)
M^-(LC/MS(ESI)): 589.1; M^+(LC/MS(ESI)): 591.3
HPLC (Condition A), Rt: 6.58 min (HPLC purity: 99.9 %).

Example 25: {({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl) benzyl]-amino}(oxo)acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt
The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine and {({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid gave the title compound as a white powder (92 %).
M^-(LC/MS(ESI)): 589.1; M^+(LC/MS(ESI)): 591.3
HPLC (Condition A), Rt: 6.58 min (HPLC purity: 99.9 %).
Analysis calculated for $C_{27}H_{37}F_3N_2O_5S_2.C_7H_{17}NO_5$: C, 51.96; H, 6.93; N, 5.35 %. Found: C, 51.54; H, 6.96; N, 5.26 %

Example 26: [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)amino](oxo)acetic acid

Step a) Formation of tert-butyl 4-[({4-[(dodecylamino)carbonyl]benzyl}amino)methyl]-piperidine-1-carboxylate
The same procedure as employed in the preparation of Example 10, step b, but starting from 4-(aminomethyl)-1-N-Boc-piperidine gave the title compound as a colorless oil (74 %).
^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.36 (t, 1H, J=5.6 Hz), 7.76 (d, 2H, J=8.2 Hz), 7.37 (d, 2H, J=7.9 Hz), 3.90 (m, 2H), 3.71 (s, 2H), 3.22 (m, 2H), 2.66 (m, 2H), 2.33 (d, 2H, J=6.4 Hz), 1.67 (m, 2H), 1.49 (m, 3H), 1.37 (s, 9H), 1.23 (br s, 18H), 1.02-0.80 (m, 5H)
M^-(LC/MS(ESI)): 514.4; M^+(LC/MS(ESI)): 516.7

HPLC (Condition A), Rt: 4.77 min (HPLC purity: 97.8 %).

Step b) Formation of tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl} [ethoxy(oxo)-acetyl]amino}methyl)piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 10, step c, but tert-butyl 4-[({4-[(dodecylamino)carbonyl]benzyl}amino)methyl]piperidine-1-carboxylate gave the title compound as a colorless oil (97 %).

M^-(LC/MS(ESI)): 614.2; M^+(LC/MS(ESI)): 616.3

HPLC (Condition A), Rt: 6.86 min (HPLC purity: 98.6 %).

Step c) Formation of ethyl [{4-[(dodecylamino)carbonyl]benzyl}(piperidin-4-ylmethyl)-amino](oxo)acetate hydrochloride

To a cold (0°C) solution of tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy (oxo)acetyl]amino}methyl)piperidine-1-carboxylate (3.84 g, 6.24 mmol) in DCM (25 mL) was added a 4 N solution of HCl in dioxane (31.1 mL) and the resulting reaction mixture was stireed 4 h at 0°C. Evaporation of the solvents gave a white amorphous solid (73 %).

^{1}H NMR (DMDO-d_6, 300 MHz) δ 9.03 (m, 0.5H), 8.70 (m, 0.5H), 8.50 (m, 1H), 7.85 (m, 2H), 7.33 (m, 2H), 4.56 (d, 2H, J=8.9 Hz), 4.40-4.20 (m, 2H), 3.35-3.10 (m, 7H), 2.80 (m, 2H), 1.70 (m, 2H), 1.52 (m, 2H), 1.43-1.15 (m, 21H), 0.86 (m, 3H)

M^-(LC/MS(ESI)): 514.4; M^+(LC/MS(ESI)): 516.4

HPLC (Condition A), Rt: 4.68 min (HPLC purity: 99.4 %).

Step d) Formation of ethyl [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)-sulfonyl] piperidin-4-yl}methyl)amino](oxo)acetate

To a solution of ethyl [{4-[(dodecylamino)carbonyl]benzyl}(piperidin-4-ylmethyl)-amino](oxo)acetate hydrochloride (900 mg, 1.63 mmol), DIAE (527 mg, 4.07 mmol) and DMAP (20 mg, 0.16 mmol) in anhydrous THF (50 mL) was added 4-methoxybenzene-sulfonyl chloride (404 mg, 1.96 mmol) dissolved in THF (2.0 mL). The reaction mixture

was stirred 14 h at rt. The solvent was evaporated and the resulting residue was dissolved in DCM (100 mL), washed with water (20 mL) and the aqueous layer was extracted with DCM (3x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under vaccum. The crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4 to 1/1 in about 1 h) to give the title compound as a white foam (992 mg, 89 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 2H, J=8.3 Hz), 7.69 (d, 2H, J=9.2 Hz), 7.27 (t, 2H, J=7.9 Hz), 7.07 (m, 2H), 6.12 (m, 1H), 4.60 (s, 1H), 4.48 (s, 1H), 3.89 (s, 3H), 3.76 (m, 2H), 3.13 (d, 1H, J=6.8 Hz), 3.07 (d, 1H, J=7.0 Hz), 2.32-2.12 (m, 2H), 1.80-1.55 (m, 6H), 1.45-1.20 (m, 24H), 0.89 (t, 3H, J=7.9 Hz)

M^-(APCI): 684.4

HPLC (Condition A), Rt: 6.84 min (HPLC purity: 99.7 %).

Step e) Formation of [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl) sulfonyl]-4-piperidinyl}methyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 1, step e but using ethyl [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl] piperidin-4-yl}methyl)amino](oxo)acetate gave the title compound as a white powder (94 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.76 (m, 2H), 7.66 (m, 1H), 7.38 (d, 1H, J=8.3 Hz), 7.32 (d, 1H, J=7.9 Hz), 7.08 (m, 2H), 4.60 (m, 2H), 3.87 (s, 3H), 3.66 (m, 2H), 3.55 (m, 1H), 3.36 (t, 2H, J=7.1 Hz), 3.16 (m, 2H), 2.17 (m, 2H), 1.61 (m, 5H), 1.35-1.18 (m, 21H), 0.87 (t, 3H, J= 8.0 Hz)

M^-(LC/MS(ESI)): 656.2; M^+(LC/MS(ESI)): 658.3

HPLC (Condition A), Rt: 6.04 min (HPLC purity: 99.9 %).

Example 27: [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)amino](oxo)acetic acid, N-methyl-D-glucamine (1-deoxy-1-(methylamino)glucitol) salt

The same procedure as employed in the preparation of Example 2 but using N-methyl-D-glucamine and [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)amino](oxo)acetic acid gave the title compound as white pellets (94.1 %).

M^-(LC/MS(ESI)): 656.2; M^+(LC/MS(ESI)): 658.3

HPLC (Condition A), Rt: 6.04 min (HPLC purity: 99.9 %).

Analysis calculated for $C_{35}H_{51}N_3O_7S.C_7H_{17}NO_5$: C, 59.13; H, 8.03; N, 6.57 %. Found: C, 58.73; H, 8.10; N, 6.57 %

Example 28: {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl] amino}-(oxo)acetic acid

Step a) Formation of the resin-bound amines of formula (D) (See Scheme 5), e.g. the resin-bound dodecylamine

The resin PS-MB-CHO HL (Argonaut Technologies Inc., 30 mg, 1.42 mmol/g, 0.0426 mmol, 100-200 mesh) was swelled in 1 % HAc in DCE/TMOF (80/20) (1.0 mL) for 15 min at rt. Dodecylamine (24 mg, 0.128 mmol) and sodium triacetoxyborohydride (27 mg, 0.128 mmol) were added and the reaction mixture was shaken at rt for 14 h. The resin was washed successively with THF (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the resin-bound dodecylamine which was used directly in the next step.

Step b) Formation of the resin-bound amides of formula (VIII-1) (See Scheme 5, Method K), e.g. resin-bound 4-chloromethyl-N-dodecyl-benzamide.

The resin-bound dodecylamine (described in step a, 0.0426 mmol) was swelled in DCM (1.0 mL) for 15 min at rt. DIEA (28 mg, 0.213 mmol) and 4-chloromethylbenzoyl chloride (40 mg, 0.213 mmol) were added and the reaction mixture was shaken at 0°C for 2h then

14 h at rt. The resin was washed successively with THF (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the resin-bound 4-chloromethyl-N-dodecyl-benzamide which was used directly in the next step.

Step c) Formation of the resin-bound secondary amines of formula (III-1) (See Scheme 5), e.g. resin-bound N-dodecyl-4-({[1-(1-naphthyl)ethyl]amino}methyl)benzamide

The resin-bound 4-chloromethyl-N-dodecyl-benzamide (described in step b, 0.0426 mmol) was swelled in NMP (0.25 mL) for 15 min at rt. DIEA (33 mg, 0.256 mmol), tetrabutyl-ammonium iodide (94.4 mg, 0.256 mmol) and 1-naphthalen-1-yl-ethylamine (44 mg, 0.256 mmol) dissolved in NMP (0.75 mL) were added and the reaction mixture was shaken 14 h at 80°C. The resin was washed successively with THF (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the resin-bound N-dodecyl-4-({[1-(1-naphthyl)ethyl]amino}-methyl)benzamide which was used directly in the next step.

Step d) Formation of the resin-bound oxamic ester of formula (I-1) (See Scheme 1), e.g. resin-bound ethyl {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino} (oxo)acetate

The resin-bound N-dodecyl-4-({[1-(1-naphthyl)ethyl]amino}methyl)benzamide (described in step c, 0.0426 mmol) was swelled in DCM (1.0 mL) for 15 min at 0°C. DIEA (28 mg, 0.213 mmol) and chloro-oxo-acetic acid ethyl ester (29 mg, 0.213 mmol) were added and the reaction mixture was shaken 3 h at 0°C then 14 h at rt. The resin was washed successively with THF (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the

resin-bound ethyl {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino}-(oxo)acetate which was used directly in the next step.

Step e) Formation of the resin-bound oxamic acid of formula (I-1) (See Scheme 1), e.g. resin-bound {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl] amino}(oxo)acetic acid

The resin-bound ethyl {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino}-(oxo)acetate (described in step d, 0.0426 mmol) was swelled in THF (0.300 mL) for 15 min at rt. Lithium hydroxide monohydrate (36 mg, 0.852 mmol) diluted in H_2O (0.060 mL) was added and the resulting reaction mixture was shaken 14 h at rt. The resin was washed successively with THF (1x 15 min), H_2O (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the resin-bound {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)-ethyl] amino}(oxo)acetic acid which was used directly in the next step.

Step f) Cleavage of the resin-bound oxamic acid of formula (I-1); formation of the oxamic acid of formula (I1) (See Scheme 1), e.g. {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl] amino}(oxo)acetic acid

The resin-bound {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl] amino}(oxo)-acetic acid (described in step e, 0.0426 mmol) was poured in TFA/DCM 20/80 (2 mL) for 1 h at rt. The resin was filtered and the solvents were evaporated under vacuum to afford a colorless oil. The crude product was purified on a SPE column (Sorbent NH_2, Isolute® 1g, 0.71 mmol/g) as follows: the column was equilibrated with DCM (2x 10 mL) and the crude product (diluted in 1 mL DCM) was poured onto the column. The column was washed with DCM (2x 5 mL) then with dioxane (2x 5 mL) and the title compounds was finally eluted with a 2 N HCl in dioxane (2x 2 mL). Evaporation of the HCl-containing fractions under vacuum gave the title compound as a colorless oil (6.5 mg).

M^-(LC/MS(ESI)): 543.0; M^+(LC/MS(ESI)): 545.8

HPLC (Condition A), Rt: 6.67 min (HPLC purity: 99.1 %).

Example 29: [{4-[(dodecylamino)carbonyl]benzyl}(2-carboxy-1-phenylethyl) amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 2-phenylglycine ethyl ester hydrochloride in step c gave the title compound as a white powder (15 mg).

M^-(LC/MS(ESI)): 523.1; M^+(LC/MS(ESI)): 525.9

HPLC (Condition A), Rt: 5.57 min (HPLC purity: 95.7 %).

Example 30: [{4-[(dodecylamino)carbonyl]benzyl}(2-methoxy-1-methylethyl) amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 2-amino-1-methoxypropane in step c gave the title compound as a colorless oil (3.7 mg).

M^-(LC/MS(ESI)): 461.3; M^+(LC/MS(ESI)): 463.3

HPLC (Condition A), Rt: 5.9 min (HPLC purity: 98.1 %).

Example 31: (4-bromo{4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-bromoaniline in step c gave the title compound as a colorless oil (2 mg).

M^+(LC/MS(ESI)): 548.3

HPLC (Condition A), Rt: 6.44 min (HPLC purity: 90.5 %).

Example 32: ({4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using aniline in step c gave the title compound as a colorless oil (3.1 mg).

M^-(LC/MS(ESI)): 465.1; M^+(LC/MS(ESI)): 467.2

HPLC (Condition A), Rt: 6.1 min (HPLC purity: 91.9 %).

Example 33: ([2-(3-chlorophenyl)ethyl]{4-[(dodecylamino)carbonyl]benzyl} amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 2-(3-chlorophenyl)ethylamine in step c gave the title compound as a colorless oil (5 mg).

M^-(LC/MS(ESI)): 527.1; M^+(LC/MS(ESI)): 530.6

HPLC (Condition A), Rt: 6.66 min (HPLC purity: 96.1 %).

Example 34: {{4-[(dodecylamino)carbonyl]benzyl}[2-(3-methoxyphenyl)ethyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 2-(3-methoxyphenyl)ethylamine in step c gave the title compound as a yellow oil (8.9 mg).

M^-(LC/MS(ESI)): 523.1; M^+(LC/MS(ESI)): 525.3

HPLC (Condition A), Rt: 6.35 min (HPLC purity: 97.2 %).

Example 35: {{4-[(dodecylamino)carbonyl]benzyl}[((d,l)-trans-2-phenylcyclopropyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using (d,l)-trans-2-phenylcyclopropylamine hydrochloride in step c gave the title compound as a colorless oil (5.5 mg).

M^-(LC/MS(ESI)): 505.3; M^+(LC/MS(ESI)): 507.2

HPLC (Condition A), Rt: 6.42 min (HPLC purity: 80.0 %).

Example 36: ([(d,l)-trans-2-(benzyloxy)cyclopentyl]{4-[(dodecylamino)carbonyl]benzyl} amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using (d,l)-2-benzyloxycyclopentylamine in step c gave the title compound as a yellow oil (12.3 mg).

M^-(LC/MS(ESI)): 563.3; M^+(LC/MS(ESI)): 565.4

HPLC (Condition A), Rt: 6.68 min (HPLC purity: 97.7 %).

Example 37: ({4-[(dodecylamino)carbonyl]benzyl}-4-phenoxyanilino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-phenoxyaniline in step c gave the title compound as a yellow oil (11.2 mg).

M^-(LC/MS(ESI)): 557.7; M^+(LC/MS(ESI)): 559.4

HPLC (Condition A), Rt: 6.64 min (HPLC purity: 94.3 %).

Example 38: [{4-[(dodecylamino)carbonyl]benzyl}(1,2,3,4-tetrahydro-1-naphthalenyl) amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 1,2,3,4-tetrahydro-1-naphthylamine in step c gave the title compound as a colorless oil (11.6 mg).

M^-(LC/MS(ESI)): 519.0; M^+(LC/MS(ESI)): 521.0

HPLC (Condition A), Rt: 6.62 min (HPLC purity: 81.1 %).

Example 39: ((1-benzyl-4-piperidinyl){4-[(dodecylamino)carbonyl] benzyl}amino)(oxo)-acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-amino-1-benzylpiperidine in step c gave the title compound as a white powder (4.3 mg).

M^-(LC/MS(ESI)): 562.0; M^+(LC/MS(ESI)): 564.7

HPLC (Condition A), Rt: 4.69 min (HPLC purity: 68.8 %).

Example 40: {{4-[(dodecylamino)carbonyl]benzyl}[2-(4-phenoxyphenyl)ethyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-phenoxyphenethylamine in step c gave the title compound as a colorless oil (4 mg).

M^-(LC/MS(ESI)): 585.6; M^+(LC/MS(ESI)): 587.3

HPLC (Condition A), Rt: 6.91 min (HPLC purity: 97.1 %).

Example 41: {{4-[(dodecylamino)carbonyl]benzyl}[2-(2-phenoxyphenyl)ethyl] amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 2-phenoxyphenethylamine in step c gave the title compound as a colorless oil (4.7 mg).

M^-(LC/MS(ESI)): 584.9; M^+(LC/MS(ESI)): 586.9

HPLC (Condition A), Rt: 6.93 min (HPLC purity: 97.9 %).

Example 42: ((2-[1,1'-biphenyl]-4-ylethyl){4-[(dodecylamino)carbonyl] benzyl}-amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 2-(4-biphenyl)ethylamine in step c gave the title compound as a colorless oil (3.9 mg).

M^-(LC/MS(ESI)): 569.1; M^+(LC/MS(ESI)): 571.2

HPLC (Condition A), Rt: 6.92 min (HPLC purity: 96.5 %).

Example 43: (([1,1'-biphenyl]-3-ylmethyl){4-[(dodecylamino)carbonyl] benzyl}-amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 3-phenylbenzyl amine in step c gave the title compound as a colorless oil (6.2 mg).

M^-(LC/MS(ESI)): 555.7; M^+(LC/MS(ESI)): 557.0

HPLC (Condition A), Rt: 6.54 min (HPLC purity: 81 %).

Example 44: (3-(benzyloxy){4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 3-(benzyloxy)aniline in step c gave the title compound as a yellow oil (10.3 mg).

M^-(LC/MS(ESI)): 571.0; M^+(LC/MS(ESI)): 573.4

HPLC (Condition A), Rt: 6.35 min (HPLC purity: 94.5 %).

Example 45: ([4-(benzoylamino)benzyl]{4-[(dodecylamino)carbonyl] benzyl} amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-benzamidobenzylamine in step c gave the title compound as a yellow oil (1.8 mg).
M^-(LC/MS(ESI)): 598.8; M^+(LC/MS(ESI)): 600.1
HPLC (Condition A), Rt: 5.93 min (HPLC purity: 55.1 %).

Example 46: N-(carboxycarbonyl)-N-{4-[(dodecylamino)carbonyl]benzyl}-3-phenyl-beta-alanine

The same procedure as employed in the preparation of Example 28 but using dl-3-amino-3-phenylpropionic acid in step c gave the title compound as a white powder (7.5 mg).
M^-(LC/MS(ESI)): 537.7; M^+(LC/MS(ESI)): 539.0
HPLC (Condition A), Rt: 5.57 min (HPLC purity: 57.3 %).

Example 47: {{4-[(dodecylamino)carbonyl]benzyl}[4-(1,2,3-thiadiazol-4-yl)benzyl]-amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-(1,2,3-thiadiazol-4-yl)benzylamine hydrochloride in step c gave the title compound as a brown powder (7.4 mg).
M^-(LC/MS(ESI)): 562.9; M^+(LC/MS(ESI)): 565.7
HPLC (Condition A), Rt: 6.02 min (HPLC purity: 94.2 %).

Example 48: [{4-[(dodecylamino)carbonyl]benzyl}(4-pentylbenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using 4-pentyl-benzylamine hydrochloride in step c gave the title compound as a colorles oil (9.3 mg).
M^-(LC/MS(ESI)): 549.0; M^+(LC/MS(ESI)): 551.1
HPLC (Condition A), Rt: 7.04 min (HPLC purity: 97.1 %).

Example 49: [{4-[(dodecylamino)carbonyl]benzyl}(1-phenylethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28 but using d,l-α-methylbenzylamine in step c gave the title compound as a white powder (14.6 mg).

M^-(LC/MS(ESI)): 493.1; M^+(LC/MS(ESI)): 495.0

HPLC (Condition A), Rt: 6.11 min (HPLC purity: 92.1 %).

Example 50: (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

Step a) Formation of the resin-bound amines of formula (D) (See Scheme 5), e.g. the resin-bound dodecylamine

The same procedure as employed in the preparation of Example 28, step a, gave the title compound.

Step b) Formation of the resin-bound protected amines of formula (VII-1) (See Scheme 5), e.g. the resin-bound 9H-fluoren-9-ylmethyl 3-[(dodecylamino)carbonyl]benzylcarbamate

The resin-bound dodecylamine (described in step a, 0.0426 mmol) was swelled in NMP (0.25 mL) for 15 min at rt. DIEA (44 mg, 0.340 mmol), Fmoc-(3-aminomethyl)-benzoic acid (64 mg, 0.170 mmol) and PyBOP® (89 mg, 0.170 mmol) were dissolved in NMP (0.75 mL) and shaken for 15 min at rt. The solution was added to the resin and the resulting reaction mixture was was shaken 14 h at rt. The resin was washed successively with NMP (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step.

Step c) Fmoc-deprotection of the resin-bound protected amines of formula (VII-1) (See Scheme 5); e.g. formation the resin-bound 3-(aminomethyl)-N-dodecylbenzamide

The resin-bound 9H-fluoren-9-ylmethyl 3-[(dodecylamino)carbonyl]benzylcarbamate (described in step b, 0.0426 mmol) was treated with a 20 % solution (v/v) of piperidine in DMF (4 mL, 1x 5min, then again 2x 15 min with a fresh solution of piperidine in DMF). The resin was washed successively with DMF (1x 15 min), MeOH (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step..

Step d) Formation of the resin-bound secondary amines of formula (III-1) (See Scheme 5, Method L), e.g. resin-bound 3-[(benzylamino)methyl]-N-dodecylbenzamide

The resin-bound 3-(aminomethyl)-N-dodecylbenzamide (described in step c, 0.0426 mmol) was swelled in THF/TMOF 80/20 (1.0 mL) for 15 min at rt. Benzaldehyde (45 mg, 0.426 mmol) was added and the mixture was shaken 14 h at rt. The resin was washed with 10 % TMOF in anhydrous THF (2x 15 min, then 2x 60 min), then with anhydrous THF (1x 30 min). The resin was then poured in anhydrous THF (1.0 mL) and sodium triacetoxyborohydride (27 mg, 0.128 mmol) was added and the mixture was shaken 14 h at rt. The resin was washed successively with THF (1x 15 min), MeOH (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step..

Step e) Formation of the resin-bound oxamic ester of formula (I-1) (See Scheme 1), e.g. resin-bound ethyl (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate

The same procedure as employed in the preparation of Example 28, step d, but using the resin-bound 3-[(benzylamino)methyl]-N-dodecylbenzamide (described in step d, 0.0426 mmol) gave the title compound which was used directly in the next step..

Step f) Formation of the resin-bound oxamic acid of formula (I-1) (See Scheme 1), e.g. resin-bound (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28, step e, but using the resin-bound ethyl (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate (described in step e, 0.0426 mmol) gave the title compound which was used directly in the next step.

Step g) Cleavage of the resin-bound oxamic acid of formula (I-1); formation of the oxamic acid of formula (I) (See Scheme 1), e.g. (benzyl{3-[(dodecylamino)carbonyl] benzyl}amino)-(oxo)acetic acid

The same procedure as employed in the preparation of Example 28, step f, but using the resin-bound (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid (described in step f, 0.0426 mmol) gave the title compound as a yellow oil (15.5 mg).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.70-7.08 (m, 9H), 4.43 (s, 2H), 4.41 (s, 2H), 3.34-3.20 (m, 2H), 1.61-1.45 (m, 2H), 1.37-1.10 (m, 18H), 0.80 (t, J=8.6 Hz, 3H)

M^-(LC/MS(ESI)): 479.4; M^+(LC/MS(ESI)): 481.2

HPLC (Condition A), Rt: 6.28 min (HPLC purity: 80.3 %).

Example 51: {{3-[(dodecylamino)carbonyl]benzyl}[4-(methylsulfonyl)benzyl]amino}-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-(methylsulfonyl)benzaldehyde in step d gave the title compound as a yellow oil (16.2 mg).

^{1}H NMR (CD_3OD, 300 MHz) δ 8.00-7.25 (m, 8H), 4.61-4.46 (m, 4H), 3.32-3.23 (m, 2H), 3.01 (s, 3H), 1.60-1.45 (m, 2H), 1.36-1.12 (m, 18H), 0.80 (t, J=8.7 Hz, 3H)

M^-(LC/MS(ESI)): 557.0; M^+(LC/MS(ESI)): 559.1

HPLC (Condition A), Rt: 5.71 min (HPLC purity: 86.5 %).

Example 52: ((3-cyanobenzyl){3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 3-cyanobenzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 506.6

Example 53: {{3-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 548.9

Example 54: [(4-chlorobenzyl)(3-{[(4-pentylbenzyl)amino]carbonyl}benzyl)-amino](oxo)-acetic acid

The same procedure as employed in the preparation of Example 50 using 4-n-pentylbenzyl-amine hydrochloride in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-chloro-benzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 507.7

Example 55: oxo{[4-({[2-(2-thienyl)ethyl]amino}carbonyl)benzyl][4-(trifluoromethyl)-benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 50 using thiophene-2-ethylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-(trifluoro-methyl)benzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 491.6

Example 56: {benzyl[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)-methyl]amino}(oxo)acetic acid

Step a) Formation of tert-Butyl-3-bromo benzoate

To a mixture of 3-bromo benzoic acid (100g, 0.5 mol), silver carbonate (276g, 1mol) and dry molecular sieves (100 g) taken in dry CH_2Cl_2 (2 L), *tert*-butylbromide (115mL, 1mol) was added dropwise at 0°C and the reaction mixture was stirred overnight at RT. The solid was filtered and washed with dichloromethane. Organic layer was washed with 10 % aqueous solution of $NaHCO_3$ (2x 500mL), water(2x 500 mL), brine and dried. The solvent was removed under vacuum to give *tert*-butyl-3-bromobenzoate (70g, 57 %).

Step b) Formation of tert-butyl-3-(4-tolyl) bromobenzoate

To a mixture of *tert*-butyl-3-bromobenzoate (65 g, 0.25 mol), 4-tolyl boronic acid (41.3 g, 0.30 mol) and sodium carbonate (150g) in a mixture of toluene (500mL) and water (50 mL), tetrakis-triphenylphosphine palladium(0) (14.5 g, 0.05 mol) was added and the reaction mixture was refluxed overnight. Cooled to RT, toluene layer was separated. The organic layer was washed with water, brine, dried. The solvent was removed under vacuum to give *tert*-butyl-3-(4-tolyl)benzoate (62 g, 90 %).

Step c) Formation of 4-(3-tert-butoxy carbonyl phenyl) benzyl bromide

To a solution of tert-Butyl-3-(4-tolyl) benzoate (60 g, 0.22 mol) in CCl_4 (800 mL) were added NBS (47.8 g, 0.268 mol) and benzoylperoxide (10 g) and the reaction mixture was

refluxed overnight. Cooled to RT and filtered. The filtrate was concentrated to give 4-(3-*tert*-butoxy carbonyl phenyl) benzyl bromide (65 g, 84 %).

Step d) Formation of 4-(3-Carboxyphenyl)benzylamine hydrochloride

Ammonia gas was passed through a cooled solution of 4-(3-*tert*-butoxycarbonylphenyl) benzyl bromide (65 g, 0.18 mol) in methanol (2 L) for 6h. Then the reaction mixture was stirred at RT overnight. Methanol was removed under vacuum. To the residue 6N aqueous solution of HCl (200 mL) was added and stirred overnight. Concentrated completely to get 4-(3-carboxyphenyl) benzylamine as a hydrochloride salt (20 g, 41 %).

Step e) Formation of N-Fmoc-4-(3-carboxyphenyl)benzylamine

A solution of 4-(3-carboxyphenyl)benzylamine hydrochloride (20 g, 0.075 mol) in 10 % Na_2CO_3 (350 mL) and dioxane (100 mL) was cooled to 0°C with stirring. A solution of Fmoc-OSu (30.7 g, 0.091 mol) in dioxane (100 mL) was added in one portion and the reaction mixture was stirred at RT for 3h. Acidified with 1.5 N aqueous solution of HCl and extracted with EtOAc (3x 400 mL). The organic layer was washed with water (3x 500 mL), brine dried over Na_2SO_4 and concentrated, purification by column chromatography using dichloromethane/methanol (9:1) to give *N*-Fmoc-4-(3-carboxyphenyl)benzylamine (16 g). This was further purified by recrystallization from THF/ PetEther gave the title pure product (8 g).

Step f) Formation of {benzyl[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2,2-diphenyl-ethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 569.5

Example 57: {(3-cyanobenzyl)[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2,2-diphenylethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 594.4

Example 58: {(4-chlorobenzyl)[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2,2-diphenylethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-chlorobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 605.3

Example 59: {[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2,2-diphenylethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 637.4

Example 60: ((3-cyanobenzyl){[3'-({[2-(4-phenoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 4-phenoxyphenethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 610.4

Example 61: oxo{{[3'-({[2-(4-phenoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}[4-(trifluoromethyl)benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 50 using 4-phenoxyphenethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 653.4

Example 62: [(3-cyanobenzyl)({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using octylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 526.4

Example 63: [(4-chlorobenzyl)({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using octylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-chlorobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 537.4

Example 64: {({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)[4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using octylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)-benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 569.4

Example 65: {(3-cyanobenzyl)[(3'-{[(3-phenylpropyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 3-phenylpropylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 532.4

Example 66: [(3-cyanobenzyl)({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 582.5

Example 67: [(4-chlorobenzyl)({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-chlorobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 592.5

Example 68: {({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 625.5

Example 69: {benzyl[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 4-n-pentylbenzylamine hydrochloride in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and benzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 549.5

Example 70: {(3-cyanobenzyl)[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 4-n-pentylbenzylamine hydrochloride in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 574.5

Example 71: {(4-chlorobenzyl)[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 4-n-pentylbenzylamine hydrochloride in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-chlorobenzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 584.3

Example 72: oxo{[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoromethyl)benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 50 using 4-n-pentylbenzylamine hydrochloride in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.
M^+(LC/MS(ESI)): 617.5

Example 73: oxo{[(3'-{[(4-phenylbutyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoromethyl)benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 50 using 4-phenylbutylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 589.5

Example 74: {(3-cyanobenzyl)[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2-(2,4,6-trimethyl-phenyl)-ethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 3-cyanobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 560.5

Example 75: {(4-chlorobenzyl)[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2-(2,4,6-trimethyl-phenyl)-ethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-chlorobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 570.4

Example 76: {[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2-(2,4,6-trimethyl-phenyl)-ethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-(trifluoromethyl)benzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 603.5

Example 77: ((4-chlorobenzyl){[3'-({[2-(4-methoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2-(4-methoxyphenyl)ethylamine in step a, N-Fmoc-4-(3-carboxyphenyl)benzylamine in step b and 4-chlorobenzaldehyde in step d gave the title compound.

M^+(LC/MS(ESI)): 558.3

Example 78: [{4-[(dodecylamino)carbonyl]benzyl}(4-methoxybenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and p-anisaldehyde in step d gave the title compound as a yellow oil (20.2 mg).

M^-(LC/MS(ESI)): 509.2; M^+(LC/MS(ESI)): 511.3

HPLC (Condition A), Rt: 6.19 min (HPLC purity: 80.2 %).

Example 79: {{4-[(dodecylamino)carbonyl]benzyl}[4-(methylsulfonyl)benzyl]amino}-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-(methylsulfonyl)benzaldehyde in step d gave the title compound as a yellow oil (21.7 mg).

M^-(LC/MS(ESI)): 557.2; M^+(LC/MS(ESI)): 559.1

HPLC (Condition A), Rt: 5.71 min (HPLC purity: 92.3 %).

Example 80: [{3-[(dodecylamino)carbonyl]benzyl}(4-methoxybenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and p-anisaldehyde in step d gave the title compound as a yellow oil (18.3 mg).
M^-(LC/MS(ESI)): 509.4; M^+(LC/MS(ESI)): 511.2
HPLC (Condition A), Rt: 6.22 min (HPLC purity: 76.1 %).

Example 81: {{3-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 3-(trifluoromethyl)benzaldehyde in step d gave the title compound as a yellow oil (19.4 mg).
M^-(LC/MS(ESI)): 547.2; M^+(LC/MS(ESI)): 549.3
HPLC (Condition A), Rt: 6.58 min (HPLC purity: 91 %).

Example 82: ({4-[(dodecylamino)carbonyl]benzyl}{[6-(trifluoromethyl)-3-pyridinyl]-methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 6-(trifluoromethyl)pyridine-3-carboxaldehyde in step d gave the title compound as a pale yellow oil (33 mg).
M^-(LC/MS(ESI)): 548.3; M^+(LC/MS(ESI)): 550.4
HPLC (Condition A), Rt: 6.03 min (HPLC purity: 83.5 %).

Example 83: 4-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)-methyl]-benzoic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and methyl 4-formylbenzoate in step d gave the title compound as a white solid (33 mg).

M^-(LC/MS(ESI)): 523.8; M^+(LC/MS(ESI)): 525.3
HPLC (Condition A), Rt: 5.45 min (HPLC purity: 92.6 %).

Example 84: ({3-[(dodecylamino)carbonyl]benzyl}{4-[hydroxy(oxido)amino]-benzyl}-amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-nitrobenzaldehyde in step d gave the title compound as an orange oil (28 mg).
M^-(LC/MS(ESI)): 524.2; M^+(LC/MS(ESI)): 526.4
HPLC (Condition A), Rt: 6.14 min (HPLC purity: 64.5 %).

Example 85: [{3-[(dodecylamino)carbonyl]benzyl}(2-fluorobenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 2-fluorobenzaldehyde in step d gave the title compound as a yellow solid (26 mg).
M^-(LC/MS(ESI)): 497.3; M^+(LC/MS(ESI)): 499.4
HPLC (Condition A), Rt: 6.19 min (HPLC purity: 78 %).

Example 86: [{3-[(dodecylamino)carbonyl]benzyl}(2-pyridinylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 2-pyridinecarboxaldehyde in step d gave the title compound as a brown oil (29 mg).
M^-(LC/MS(ESI)): 480.3; M^+(LC/MS(ESI)): 482.4
HPLC (Condition A), Rt: 4.67 min (HPLC purity: 89 %).

Example 87: [{3-[(dodecylamino)carbonyl]benzyl}(3-thienylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 3-thiophenecarboxaldehyde in step d gave the title compound as an orange oil (24 mg).

M^-(LC/MS(ESI)): 485.2; M^+(LC/MS(ESI)): 487.4

HPLC (Condition A), Rt: 6.13 min (HPLC purity: 64 %).

Example 88: [{3-[(dodecylamino)carbonyl]benzyl}(4-hydroxybenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-hydroxybenzaldehyde in step d gave the title compound as an orange oil (29 mg).

M^-(LC/MS(ESI)): 495.3; M^+(LC/MS(ESI)): 497.3

HPLC (Condition A), Rt: 5.55 min (HPLC purity: 81.1 %).

Example 89: [{3-[(dodecylamino)carbonyl]benzyl}(4-phenoxybenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-phenoxybenzaldehyde in step d gave the title compound as a yellow oil (30 mg).

M^-(LC/MS(ESI)): 571.5; M^+(LC/MS(ESI)): 573.3

HPLC (Condition A), Rt: 6.68 min (HPLC purity: 77.3 %).

Example 90: ({3-[(dodecylamino)carbonyl]benzyl}{[6-(trifluoromethyl)-3-pyridinyl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 6-(trifluoromethyl)pyridine-3-carboxaldehyde in step d gave the title compound as a pale yellow oil (32 mg).
M^+(LC/MS(ESI)): 550.5
HPLC (Condition A), Rt: 6.19 min (HPLC purity: 79.8 %).

Example 91: 3-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]-benzoic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 3-carboxybenzaldehyde in step d gave the title compound as a pale yellow oil (33 mg).
M^+(LC/MS(ESI)): 525.3
HPLC (Condition A), Rt: 5.53 min (HPLC purity: 76 %).

Example 92: 5-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]-2-thiophenecarboxylic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 5-formyl-2-thiophenecarboxylic acid in step d gave the title compound as a pale yellow oil (31 mg).
M^-(LC/MS(ESI)): 529.2; M^+(LC/MS(ESI)): 531.2
HPLC (Condition A), Rt: 5.32 min (HPLC purity: 54 %).

Example 93: ({4-[(dodecylamino)carbonyl]benzyl}{4-[hydroxy(oxido)amino]benzyl}-amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-nitrobenzaldehyde in step d gave the title compound as a brown oil (28 mg).

M^-(LC/MS(ESI)): 524.2; M^+(LC/MS(ESI)): 526.3
HPLC (Condition A), Rt: 6 min (HPLC purity: 58.5 %).

Example 94: ((1,3-benzodioxol-5-ylmethyl){4-[(dodecylamino)carbonyl]-benzyl}amino)-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and piperonal in step d gave the title compound as an orange oil (27 mg).
M^-(LC/MS(ESI)): 523.2; M^+(LC/MS(ESI)): 526.4
HPLC (Condition A), Rt: 6.08 min (HPLC purity: 59.8 %).

Example 95: [{4-[(dodecylamino)carbonyl]benzyl}(2-fluorobenzyl)amino](oxo)acetic acid
The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 2-fluorobenzaldehyde in step d gave the title compound as a yellow solid (30 mg).
M^-(LC/MS(ESI)): 497.3; M^+(LC/MS(ESI)): 499.5
HPLC (Condition A), Rt: 6.2 min (HPLC purity: 79.1 %).

Example 96: [{4-[(dodecylamino)carbonyl]benzyl}(4-phenoxybenzyl)amino](oxo)acetic acid
The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-phenoxybenzaldehyde in step d gave the title compound as a pale yellow oil (28 mg).
M^-(LC/MS(ESI)): 571.2; M^+(LC/MS(ESI)): 573.4
HPLC (Condition A), Rt: 6.67 min (HPLC purity: 64.5 %).

Example 97: 4-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)-methyl]-benzoic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and methyl 4-formylbenzoate in step d gave the title compound as a white solid (28 mg).
M^-(LC/MS(ESI)): 523.2; M^+(LC/MS(ESI)): 525.2
HPLC (Condition A), Rt: 5.49 min (HPLC purity: 62.9 %).

Example 98: 5-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]-2-thiophenecarboxylic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 5-formyl-2-thiophenecarboxylic acid in step d gave the title compound as a pale yellow oil (28 mg).
M^-(LC/MS(ESI)): 529.2; M^+(LC/MS(ESI)): 531.7
HPLC (Condition A), Rt: 5.37 min (HPLC purity: 58 %).

Example 99: [{3-[(dodecylamino)carbonyl]benzyl}(2-thienylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 2-thiophenecarboxaldehyde in step d gave the title compound as a colorless oil (6.8 mg).
M^-(LC/MS(ESI)): 485.4; M^+(LC/MS(ESI)): 487.3
HPLC (Condition A), Rt: 6.11 min (HPLC purity: 97.6 %).

Example 100: [{4-[(dodecylamino)carbonyl]benzyl}(isopropyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, 4-chloromethylbenzoyl chloride in step b and isopropylamine in step d gave the title compound as a pale yellow oil (21 mg).
M^-(LC/MS(ESI)): 431.3; M^+(LC/MS(ESI)): 433.3
HPLC (Condition A), Rt: 4.12 min (HPLC purity: 85.5 %).

Example 101: ((3,5-dichlorobenzyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, 4-chloromethylbenzoyl chloride in step b and 3,5-dichlorobenzylamine in step d gave the title compound as a pale yellow oil (24 mg).
M^-(LC/MS(ESI)): 547.2; M^+(LC/MS(ESI)): 551.1
HPLC (Condition A), Rt: 6.61 min (HPLC purity: 82 %).

Example 102: [(3,5-dichlorobenzyl)(4-{[(3,3-diphenylpropyl)amino]carbonyl}-benzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 3,3-diphenylpropylamine in step a, 4-chloromethylbenzoyl chloride in step b and 3,5-dichlorobenzylamine in step d gave the title compound as a pale yellow oil (22 mg).
M^-(LC/MS(ESI)): 573.0; M^+(LC/MS(ESI)): 575.0
HPLC (Condition A), Rt: 5.13 min (HPLC purity: 81.2 %).

Example 103: [(4-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]carbonyl}benzyl)(3,5-dichlorobenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2-(4-biphenyl)ethylamine in step a, 4-chloromethylbenzoyl chloride in step b and 3,5-dichlorobenzylamine in step d gave the title compound as a pale yellow oil (21 mg).

M^-(LC/MS(ESI)): 559.6

HPLC (Condition A), Rt: 5.06 min (HPLC purity: 79.7 %).

Example 104: [(1,3-benzodioxol-5-ylmethyl)(4-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]-carbonyl}benzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 2-(4-biphenyl)-ethylamine in step a, 4-chloromethylbenzoyl chloride in step b and piperonylamine in step d gave the title compound as a pale yellow oil (23 mg).

M^-(LC/MS(ESI)): 535.1; M^+(LC/MS(ESI)): 537.0

HPLC (Condition A), Rt: 4.46 min (HPLC purity: 79.1 %).

Example 105: (2,3-dihydro-1H-inden-1-yl{4-[(dodecylamino)carbonyl]benzyl}-amino)-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, 4-chloromethylbenzoyl chloride in step b and 1-aminoindane in step d gave the title compound as a pale yellow oil (23 mg).

M^-(LC/MS(ESI)): 505.2; M^+(LC/MS(ESI)): 507.7

HPLC (Condition A), Rt: 6.28 min (HPLC purity: 67.9 %).

Example 106: {2,3-dihydro-1H-inden-1-yl[4-({[2-(4-phenoxyphenyl)ethyl]amino}-carbonyl)benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using 4-phenoxy-phenethylamine in step a, 4-chloromethylbenzoyl chloride in step b and 1-aminoindane in step d gave the title compound as a pale yellow oil (21 mg).

M^-(LC/MS(ESI)): 533.3; M^+(LC/MS(ESI)): 535.0

HPLC (Condition A), Rt: 4.67 min (HPLC purity: 67.3 %).

Example 107: [{4-[(dodecylamino)carbonyl]benzyl}(4-pyridinylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-pyridinecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white solid (5 mg).

M^-(LC/MS(ESI)): 480.3; M^+(LC/MS(ESI)): 482.3

HPLC (Condition A), Rt: 4.35 min (HPLC purity: 93.7 %).

Example 108: ([4-(dimethylamino)benzyl]{4-[(dodecylamino)carbonyl]benzyl}amino)-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-dimethylaminobenzaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a brown oil (2 mg).

M^-(LC/MS(ESI)): 522.3; M^+(LC/MS(ESI)): 524.6

HPLC (Condition A), Rt: 4.57 min (HPLC purity: 80.5 %).

Example 109: [{4-[(dodecylamino)carbonyl]benzyl}(3-pyridinylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 3-pyridinecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white solid (6 mg).

M^-(LC/MS(ESI)): 480.3; M^+(LC/MS(ESI)): 482.5

HPLC (Condition A), Rt: 4.41 min (HPLC purity: 86.8 %).

Example 110: ((4-cyanobenzyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-cyanobenzaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a yellow oil (6 mg).

M^-(LC/MS(ESI)): 504.4; M^+(LC/MS(ESI)): 506.2

HPLC (Condition A), Rt: 5.85 min (HPLC purity: 87.3 %).

Example 111: [{4-[(dodecylamino)carbonyl]benzyl}(1,3-thiazol-2-ylmethyl)amino](oxo)-acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 2-formylthiazole in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a yellow oil (4 mg).

M^-(APCI): 486.2; M^+(APCI): 488.2

HPLC (Condition A), Rt: 5.48 min (HPLC purity: 85.4 %).

Example 112: ({4-[(dodecylamino)carbonyl]benzyl}{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 2-morpholino-1,3-thiazole-5-carbaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as an orange oil (5 mg).

M^-(LC/MS(ESI)): 571.3; M^+(LC/MS(ESI)): 573.4

HPLC (Condition A), Rt: 4.62 min (HPLC purity: 97.7 %).

Example 113: [{3-[(dodecylamino)carbonyl]benzyl}(4-pyridinylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-pyridinecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as an orange oil (5 mg).

M^-(LC/MS(ESI)): 480.5; M^+(LC/MS(ESI)): 482.3

HPLC (Condition A), Rt: 4.34 min (HPLC purity: 89.7 %).

Example 114: [{3-[(dodecylamino)carbonyl]benzyl}(3-pyridinylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 3-pyridinecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a yellow oil (7 mg).

M^-(LC/MS(ESI)): 480.4; M^+(LC/MS(ESI)): 482.3

HPLC (Condition A), Rt: 4.36 min (HPLC purity: 89.7 %).

Example 115: [{3-[(dodecylamino)carbonyl]benzyl}(3-hydroxybenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 3-hydroxybenzaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a yellow oil (4 mg).

M^-(LC/MS(ESI)): 495.4; M^+(LC/MS(ESI)): 497.3

HPLC (Condition A), Rt: 5.58 min (HPLC purity: 82.5 %).

Example 116: ((4-cyanobenzyl){3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 4-cyanobenzaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as an orange oil (5 mg).

M^-(LC/MS(ESI)): 504.3; M^+(LC/MS(ESI)): 506.3

HPLC (Condition A), Rt: 5.86 min (HPLC purity: 97.5 %).

Example 117: [{3-[(dodecylamino)carbonyl]benzyl}(1,3-thiazol-2-ylmethyl)amino]-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 2-formylthiazole in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a red oil (4 mg).

M^-(LC/MS(ESI)): 486; M^+(LC/MS(ESI)): 488.5

HPLC (Condition A), Rt: 5.49 min (HPLC purity: 68.3 %).

Example 118: ({3-[(dodecylamino)carbonyl]benzyl}{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and 2-morpholino-1,3-thiazole-5-carbaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as an orange oil (4 mg).

M^-(LC/MS(ESI)): 571.4; M^+(LC/MS(ESI)): 573.0

HPLC (Condition A), Rt: 4.59 min (HPLC purity: 96.3 %).

Example 119: ((1,3-benzodioxol-5-ylmethyl){3-[(dodecylamino)carbonyl]benzyl}amino)-(oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(3-aminomethyl)-benzoic acid in step b and piperonal in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white solid (6.3 mg).

M^-(LC/MS(ESI)): 523.3; M^+(LC/MS(ESI)): 525.4

HPLC (Condition A), Rt: 6.07 min (HPLC purity: 97.4 %).

Example 120: [{4-[(dodecylamino)carbonyl]benzyl}(2-thienylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 2-thiophenecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white powder (2.4 mg).

M^-(LC/MS(ESI)): 485.2; M^+(LC/MS(ESI)): 487.4

HPLC (Condition A), Rt: 5.9 min (HPLC purity: 90.4 %).

Example 121: [{4-[(dodecylamino)carbonyl]benzyl}(2-pyridinylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 2-pyridinecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white powder (5.0 mg).

M^-(LC/MS(ESI)): 480.5; M^+(LC/MS(ESI)): 482.4

HPLC (Condition A), Rt: 4.66 min (HPLC purity: 96.3 %).

Example 122: [{4-[(dodecylamino)carbonyl]benzyl}(3-thienylmethyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 3-thiophenecarboxaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white powder (2.6 mg).
M^-(LC/MS(ESI)): 485.4; M^+(LC/MS(ESI)): 487.4
HPLC (Condition A), Rt: 5.9 min (HPLC purity: 95 %).

Example 123: [{4-[(dodecylamino)carbonyl]benzyl}(4-hydroxybenzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 4-hydroxybenzaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a white powder (3.3 mg).
M^-(LC/MS(ESI)): 495.4; M^+(LC/MS(ESI)): 497.3
HPLC (Condition A), Rt: 5.47 min (HPLC purity: 95.3 %).

Example 124: 3-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)-methyl]-benzoic acid

The same procedure as employed in the preparation of Example 50 using dodecylamine in step a, Fmoc-(4-aminomethyl)-benzoic acid in step b and 3-carboxybenzaldehyde in step d gave a crude product which was purified by reverse phase HPLC chromatography (Condition C) affording the title compound as a colorless oil (5.7 mg).
M^-(LC/MS(ESI)): 523.2; M^+(LC/MS(ESI)): 525.4
HPLC (Condition A), Rt: 5.43 min (HPLC purity: 95.5 %).

Example 125: [benzyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

Step a) Formation of the resin-bound amines of formula (D) (See Scheme 5), e.g. the resin-bound dodecylamine

The same procedure as employed in the preparation of Example 28, step a, gave the title compound which was used directly in the next step.

Step b) Formation of the resin-bound protected amines of formula (VII-1) (See Scheme 5, Method L), e.g. the resin-bound 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-N-dodecyl-thiophene-2-sulfonamide

The resin-bound dodecylamine (described in step a, 0.0426 mmol) was swelled in DCM (1.0 mL) for 15 min at rt. DIEA (33 mg, 0.256 mmol) and 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]thiophene-2-sulfonyl chloride (44 mg, 0.128 mmol) were added and the resulting reaction mixture was was shaken 14 h at rt. The resin was washed successively with NMP (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step.

Step c) Phtalimide-deprotection of the resin-bound protected amines of formula (VII-1) (See Scheme 5); e.g formation of the resin-bound 5-(aminomethyl)-N-dodecylthiophene-2-sulfonamide

The resin-bound 5-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-N-dodecylthiophene-2-sulfonamide (described in step b, 0.0426 mmol) was treated with a 60 % solution (v/v) hydrazine monohydrate in DMF (1.15 mL) and shaken 14 h at rt.The resin was washed successively with DMF (1x 15 min), MeOH (1x 15 min), MeOH (3x 10 min), DMF (3x 10

min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step.

Step d) Formation of the resin-bound secondary amines of formula (III-1) (See Scheme 5, Method L), e.g. the resin-bound 5-[(benzylamino)methyl]-N-dodecylthiophene-2-sulfonamide

The same procedure as employed in the preparation of Example 50, step d, using benzaldehyde and the resin-bound 5-(aminomethyl)-N-dodecylthiophene-2-sulfonamide (described in step c, 0.0426 mmol) gave the title compound which was used directly in the next step.

Step e) Formation of the resin-bound oxamic ester of formula (I-1) (See Scheme 1), e.g. resin-bound ethyl [benzyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate

The same procedure as employed in the preparation of Example 28, step d, but using the resin-bound 5-[(benzylamino)methyl]-N-dodecylthiophene-2-sulfonamide (described in step d, 0.0426 mmol) gave the title compound which was used directly in the next step.

Step f) Formation of the resin-bound oxamic acid of formula (I-1) (See Scheme 1), e.g. resin-bound [benzyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28, step e, but using the resin-bound ethyl [benzyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate (described in step e, 0.0426 mmol) gave the title compound which was used directly in the next step.

Step g) Cleavage of the resin-bound oxamic acid of formula (I-1); formation of the oxamic acid of formula (I) (See Scheme 1), e.g. [benzyl({5-[(dodecylamino)sulfonyl]-2-thienyl}-methyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 28, step f, but using the resin-bound [benzyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid (described in step f, 0.0426 mmol) gave the title compound as a white gum (20 mg).
M^-(LC/MS(ESI)): 521.2; M^+(LC/MS(ESI)): 523.0
HPLC (Condition A), Rt: 6.17 min (HPLC purity: 86.2 %).

Example 126: [cyclopentyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

Step a) Formation of the resin-bound 5-[(cyclopentylamino)methyl]-N-dodecylthiophene-2-sulfonamide

The resin-bound 5-(aminomethyl)-N-dodecylthiophene-2-sulfonamide (Example 125, step c, 0.23 mmol) was swelled in a 1 % HAc in DMF mixture for 15 min at rt. Cyclopentanone (97 mg, 1.15 mmol) and sodium cyanoborohydride (144 mg, 2.3 mmol) were then added and the reaction mixture shaken 14 h at rt. The resin was washed successively with DMF (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step.

Step b) Formation of the resin-bound ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate

The same procedure as employed in the preparation of Example 28, step d but using resin-bound 5-[(cyclopentylamino)methyl]-N-dodecylthiophene-2-sulfonamide gave the title compound which was used directly in the next step.

Step c) Cleavage of the resin bound ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate; formation of the ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate

The same procedure as employed in the preparation of Example 28, step f but using resin-bound ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate gave a yellow oil. This crude product was purified by column chromatography over silica gel to give the title compound (11 mg, 10 %).

M^-(LC/MS(ESI)): 527.2; M^+(LC/MS(ESI)): 529.4

HPLC (Condition A), Rt: 6.94 min (HPLC purity: 91.0 %).

Step d) Formation of [cyclopentyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 1, step e but using ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate gave the title compound as a colorless foam (96 %).

^{1}H NMR (CD_3OD, 300 MHz) δ 7.25 (m, 1H), 7.0 (m, 1H), 4.64 (s, 1H), 4.30 (m, 1H), 2.76 (t, 2H, J=7.3Hz), 1.81 (m, 2H), 1.79-1.41 (m, 8H), 1.29 (m, 19H), 0.91 (t, 3H, J=6.8 Hz)

M^-(LC/MS(ESI)): 499.2; M^+(LC/MS(ESI)): 501.2

HPLC (Condition A), Rt: 6.09 min (HPLC purity: 78.7 %).

Example 127: (({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl){3-[hydroxy(oxido)-amino]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 3-nitrobenzaldehyde in step d gave the title compound as an orange oil (29 mg).

M^-(LC/MS(ESI)): 566.3; M^+(LC/MS(ESI)): 568.2

HPLC (Condition A), Rt: 6.23 min (HPLC purity: 61.7 %).

Example 128: [({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(4-methoxybenzyl)amino]-(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and p-anisaldehyde in step d gave the title compound as a yellow oil (27 mg).
M^-(LC/MS(ESI)): 551.2; M^+(LC/MS(ESI)): 553.4
HPLC (Condition A), Rt: 6.26 min (HPLC purity: 73.3 %).

Example 129: [({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(2-fluorobenzyl)amino]-(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 2-fluorobenzaldehyde in step d gave the title compound as a yellow solid (28 mg).
M^-(LC/MS(ESI)): 539.1; M^+(LC/MS(ESI)): 541.2
HPLC (Condition A), Rt: 6.33 min (HPLC purity: 70 %).

Example 130: {({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(methylsulfonyl)-benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 4-(methylsulfonyl)benzaldehyde in step d gave the title compound as a yellow oil (36 mg).
M^-(LC/MS(ESI)): 599.2; M^+(LC/MS(ESI)): 601.3
HPLC (Condition A), Rt: 5.81 min (HPLC purity: 69.4 %).

Example 131: [({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(4-phenoxybenzyl)amino]-(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 4-phenoxybenzaldehyde in step d gave the title compound as a yellow oil (33 mg).
M^-(LC/MS(ESI)): 613.2; M^+(LC/MS(ESI)): 615.0
HPLC (Condition A), Rt: 6.78 min (HPLC purity: 68.5 %).

Example 132: 4-{[(carboxycarbonyl)({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)-amino]methyl}benzoic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and methyl 4-formylbenzoate in step d gave the title compound as a yellow oil (5 mg).
M^-(LC/MS(ESI)): 565.3; M^+(LC/MS(ESI)): 567.3
HPLC (Condition A), Rt: 5.43 min (HPLC purity: 99.9 %).

Example 133: (({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl){[6-(trifluoromethyl)-3-pyridinyl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 6-(trifluoromethyl)pyridine-3-carboxaldehyde in step d gave the title compound as an orange oil (30 mg).
M^-(LC/MS(ESI)): 590.3; M^+(LC/MS(ESI)): 592.2
HPLC (Condition A), Rt: 6.25 min (HPLC purity: 61.7 %).

Example 134: {({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[3-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 3-(trifluoromethyl)benzaldehyde in step d gave the title compound as a yellow oil (19 mg).
M^-(LC/MS(ESI)): 589.3; M^+(LC/MS(ESI)): 591.3
HPLC (Condition A), Rt: 6.43 min (HPLC purity: 81.5 %).

Example 135: [(3-chlorobenzyl)({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino]-(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using dodecylamine in step a and 3-chlorobenzaldehyde in step d gave the title compound as a yellow oil (21 mg).
M^-(LC/MS(ESI)): 556; M^+(LC/MS(ESI)): 558
HPLC (Condition A), Rt: 6.32 min (HPLC purity: 81.9 %).

Example 136: {[(5-{[(3,3-diphenylpropyl)amino]sulfonyl}-2-thienyl)methyl][3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using 3,3-diphenylpropylamine in step a and 3-(trifluoromethyl)benzaldehyde in step d gave the title compound as a yellow oil (17 mg).
M^-(LC/MS(ESI)): 615.3; M^+(LC/MS(ESI)): 617.3
HPLC (Condition A), Rt: 5.12 min (HPLC purity: 75.7 %).

Example 137: {(3-chlorobenzyl)[(5-{[(3,3-diphenylpropyl)amino]sulfonyl}-2-thienyl)-methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using 3,3-diphenylpropylamine in step a and 3-chlorobenzaldehyde in step d gave the title compound as a yellow oil (15 mg).
M^-(LC/MS(ESI)): 582.5; M^+(LC/MS(ESI)): 585.1
HPLC (Condition A), Rt: 5.01 min (HPLC purity: 72.1 %).

Example 138: oxo{{[5-({[2-(4-phenoxyphenyl)ethyl]amino}sulfonyl)-2-thienyl]methyl}[3-(trifluoromethyl)benzyl]amino}acetic acid

The same procedure as employed in the preparation of Example 125 using 4-phenoxyphenethylamine in step a and 3-(trifluoromethyl)benzaldehyde in step d gave the title compound as a yellow oil (22 mg).
M^-(LC/MS(ESI)): 617.0; M^+(LC/MS(ESI)): 619.0
HPLC (Condition A), Rt: 5.15 min (HPLC purity: 77.1 %).

Example 139: ((3-chlorobenzyl){[5-({[2-(4-phenoxyphenyl)ethyl]amino}sulfonyl)-2-thienyl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using 4-phenoxyphenethylamine in step a and 3-chlorobenzaldehyde in step d gave the title compound as a yellow oil (20 mg).
M^-(LC/MS(ESI)): 584; M^+(LC/MS(ESI)): 586
HPLC (Condition A), Rt: 5.0 min (HPLC purity: 79 %).

Example 140: {[(5-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]sulfonyl}-2-thienyl)methyl][3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 125 using 2-(4-biphenyl)-ethylamine in step a and 3-(trifluoromethyl)benzaldehyde in step d gave the title compound as a yellow oil (20 mg).
M^-(LC/MS(ESI)): 601.2; M^+(LC/MS(ESI)): 603.0
HPLC (Condition A), Rt: 5.13 min (HPLC purity: 71.4 %).

Example 141: (({1-[(cyclohexylamino)carbonyl]-4-piperidinyl}methyl){4-[(dodecyl-amino)carbonyl]benzyl}amino)(oxo)acetic acid

Step a) Formation of tert-butyl 4-[({4-[(benzyloxy)carbonyl]benzyl}amino)methyl]-piperidine-1-carboxylate
The same procedure as employed in the preparation of Example 1, step a but using 4-(aminomethyl)-1-Boc-piperidine gave the title compound as a white solid (8.045 g, 63 %).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, 2H, J=8.3 Hz), 7.45-7.30 (m, 7H), 5.35 (s, 2H), 4.10 (m, 2H), 3.83 (s, 2H), 2.67 (t, 2H, J=12.3 Hz), 2.48 (d, 2H, J=6.5 Hz), 1.70 (d, 2H, J=13.4 Hz), 1.59 (m, 1H), 1.43 (s, 9H), 1.16-1.02 (m, 2H)
M^+(LC/MS (ESI)): 439.6
HPLC (Condition A), Rt: 3.66 min (HPLC purity: 91.9 %).

Step b) Formation of tert-butyl 4-({{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]-amino}methyl)piperidine-1-carboxylate
The same procedure as employed in the preparation of Example 1, step b but using tert-butyl 4-[({4-[(benzyloxy)carbonyl]benzyl}amino)methyl]piperidine-1-carboxylate gave the title compound as a yellow foam (8.50 g, 87 %).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H), 7.46-7.29 (m, 7H), 5.35 (br s, 2H), 4.67 (s, 1H), 4.52 (s, 1H), 4.39-4.25 (m, 2H), 4.10 (m, 2H), 3.08 (d, 1H, J=7.1 Hz), 2.61 (m, 2H), 1.90-1.65 (m, 1H), 1.57 (m, 2H), 1.43 (s, 9H), 1.36 (t, 2H, J=7.1 Hz), 1.20-1.02 (m, 2H)

M^-(LC/MS (ESI)): 537.8; M^+(LC/MS (ESI)): 539.5
HPLC (Condition A), Rt: 5.68 min (HPLC purity: 98.4 %).

Step c) Deprotection of tert-butyl 4-({{4-[(benzyloxy)carbonyl]benzyl}-[ethoxy(oxo)-acetyl]amino}methyl)piperidine-1-carboxylate; formation of 4-({{[1-(tert-butoxy-carbonyl)piperidin-4-yl]methyl}[ethoxy(oxo)acetyl]-amino}methyl)benzoic acid
The same procedure as employed in the preparation of Example 1, step c but using tert-butyl 4-({{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl] amino}methyl)piperidine-1-carboxylate gave the title compound as a white foam (6.80 g, 96 %).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (m, 2H), 7.37 (m, 2H), 4.70 (s, 1H), 4.55 (s, 1H), 4.40-4.20 (m, 2H), 4.09 (m, 2H), 3.40-3.10 (m, 2H), 3.62 (m, 2H), 1.90-1.68 (m, 1H), 1.59 (m, 2H), 1.43 (s, 9H), 1.30-1.00 (m, 5H)
M^-(APCI): 447.0
HPLC (Condition A), Rt: 4.31 min (HPLC purity: 98.4 %).

Step d) Formation of 4-{[[ethoxy(oxo)acetyl](piperidin-4-ylmethyl)amino]methyl} benzoic acid
To a solution of 4-({{[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl}[ethoxy(oxo)acetyl]-amino}methyl)benzoic acid (5.80 g, 12.93 mmol) in DCM (150 mL) was added TFA (9.90 mL) and the resulting reaction mixture was stirred at rt for 3 h, evaporated under vacuum to give the title compound as a pink oil (7.93 g, 99.9 %).
^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.7 (m, 1H), 8.39 (m, 1H), 7.96 (d, 1H, J=8.3 Hz), 7.94 (d, 1H, J=8.3 Hz), 7.39 (d, 1H, J=8.3 Hz), 7.37 (d, 1H, J=8.3 Hz), 4.64 (s, 1H), 4.58 (s, 1H), 4.33 (q, 0.9H, J=7.2 Hz), 4.23 (q, 1.1H, J=7.2 Hz), 3.33-3.22 (m , 2H), 3.18 (d, 1H, J=7.6 Hz), 3.10 (d, 1H, J=7.2 Hz), 2.90-2.69 (m, 2H), 1.98 (m, 1H), 1.40-1.21 (m, 3H), 1.16 (t, 2H, J=7.1 Hz)
HPLC (Condition A), Rt: 1.87 min (HPLC purity: 98.9 %).

Step e) Formation of 4-{[[ethoxy(oxo)acetyl]({1-[(9H-fluoren-9-ylmethoxy)carbonyl] piperidin-4-yl}methyl)amino]methyl}benzoic acid

To a solution of 4-{[[ethoxy(oxo)acetyl](piperidin-4-ylmethyl)amino]methyl}benzoic acid (7.650g, 16.54 mmol) in dioxane/H_2O (1/1) (120 mL) was added Fmoc-OSu (6.697 g, 19.85 mmol) and a 1 M aqueous solution of $NaHCO_3$ (10 mL). The resulting reaction mixture was stirred for 1,25 h, then concentrated under vacuum. The oily residue dissolved in DCM (120 mL) was washed with a 1 N aqueous solution until pH 1, dried over $MgSO_4$, filtered and the solvents were evaporated under vacuum. This crude product was purified by column chromatography over silica gel (AcOEt/c-Hex 1/4 to 1/1 in about 1h) to give the title compound as a white powder (3.755 g, 40 %).

^1H NMR ($CDCl_3$, 300 MHz) δ 8.1 (m, 2H), 7.75 (d, 2H, J=7.6 Hz), 7.55 (d, 2H, J=7.2 Hz), 7.38 (m, 4H), 7.29 (t, 2H, J=7.3 Hz), 4.70 (s, 1H), 4.56 (s, 1H), 4.45-4.07 (m, 7H), 3.0 (m, 2H), 2.45 (m, 2H), 1.7-1.5 (m, 1H), 1.40 (m, 2H), 1.38 (t, 1H, J=7.0 Hz), 1.31-1.21 (m, 3H), 1.0-0.8 (m, 2H)

M^-(LC/MS (ESI)): 569.4; M^+(LC/MS (ESI)): 571.8

HPLC (Condition A), Rt: 4.83 min (HPLC purity: 99.3 %).

Step f) Formation of the resin-bound dodecylamine

The same procedure as employed in the preparation of Example 28, step a, gave the title compound which was used directly in the next step.

Step g) Formation of the resin-bound 9H-fluoren-9-ylmethyl 4-({{4-[(dodecylamino)-carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}methyl)piperidine-1-carboxylate

The same procedure as employed in the preparation of Example 50, step b using 4-{[[ethoxy(oxo)acetyl]({1-[(9H-fluoren-9-ylmethoxy)carbonyl]piperidin-4-yl}methyl)-amino]methyl}benzoic acid and the resin-bound dodecylamine gave the title compound.

Step h) Formation of the resin-bound ethyl [{4-[(dodecylamino)carbonyl]benzyl}(piperidin -4-ylmethyl)amino](oxo)acetate

The same procedure as employed in the preparation of Example 50, step c using the resin-bound 9H-fluoren-9-ylmethyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)-acetyl]amino}methyl)piperidine-1-carboxylate gave the title compound which was used directly in the next step.

Step i) Formation of the resin bound ethyl (({1-[(cyclohexylamino)carbonyl]piperidin-4-yl}methyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate

The resin-bound ethyl [{4-[(dodecylamino)carbonyl]benzyl}(piperidin-4-ylmethyl)amino](oxo)acetate (described in step h, 0.0426 mmol) was swelled in THF (0.5 mL) for 15 min at rt. Cyclohexyl isocyanate (18 mg, 0.143 mmol) dissolved in THF (0.9 mL) and TEA (29 mg, 0.282 mmol) was added and the reaction mixture was shaken 14 h at rt. The resin was washed successively with THF (1x 15 min), MeOH (1x 15 min), THF (1x 15 min), MeOH (3x 10 min), DMF (3x 10 min), MeOH (1x 5 min), THF (3x 10 min), MeOH (1x 5 min), DCM (3x 10 min) and with Et_2O (1x 10 min). The resin was then dried under vacuum to afford the title compound which was used directly in the next step.

Step j) Formation of the resin-bound (({1-[(cyclohexylamino)carbonyl]-4-piperidinyl}-methyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28, step e, but using the resin-bound ethyl (({1-[(cyclohexylamino)carbonyl]piperidin-4-yl}methyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate (described in step i, 0.0426 mmol) gave the title compound which was used directly in the next step.

Step k) Formation of the (({1-[(cyclohexylamino)carbonyl]-4-piperidinyl}methyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 28, step f, but using the resin-bound (({1-[(cyclohexylamino)carbonyl]-4-piperidinyl}methyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid (described in step j, 0.0426 mmol) gave the title compound as a white solid (23 mg).

M^-(ESI): 611.4; M^+(ESI): 613.4

HPLC (Condition A), Rt: 5.9 min (HPLC purity: 93.1 %).

Example 142: ([(1-{[4-(dimethylamino)anilino]carbonyl}-4-piperidinyl)methyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using dodecylamine in step f and 4-(dimethylamino)phenyl isocyanate in step i gave the title compound as a brown oil (17 mg).

M^-(ESI): 648.2; M^+(ESI): 650.4

HPLC (Condition A), Rt: 4.49 min (HPLC purity: 95.9 %).

Example 143: {{4-[(dodecylamino)carbonyl]benzyl}[(1-hexanoyl-4-piperidinyl)-methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using dodecylamine in step f and hexanoyl chloride in step i gave the title compound as a yellow oil (17 mg).

M^-(ESI): 584.4; M^+(ESI): 586.4

HPLC (Condition A), Rt: 6.06 min (HPLC purity: 83.3 %).

Example 144: ({4-[(dodecylamino)carbonyl]benzyl}{[1-(3-iodobenzoyl)-4-piperidinyl]-methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using dodecylamine in step f and 3-iodobenzoyl chloride in step i gave the title compound as a brown solid (14 mg).
M^-(ESI): 716.2
HPLC (Condition A), Rt: 6.12 min (HPLC purity: 90.8 %).

Example 145: {{4-[(dodecylamino)carbonyl]benzyl}[(1-{(2E)-3-[3-(trifluoromethyl)-phenyl]-2-propenoyl}-4-piperidinyl)methyl]amino}(oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using dodecylamine in step f and trans-3-(trifluoromethyl)cinnamoyl chloride in step i gave the title compound as a white foam (19 mg).
M^-(ESI): 684.2; M^+(ESI): 686.4
HPLC (Condition A), Rt: 6.28 min (HPLC purity: 95 %).

Example 146: ({4-[(dodecylamino)carbonyl]benzyl}{[1-(2-quinoxalinylcarbonyl)-4-piperidinyl]methyl}amino)(oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using dodecylamine in step f and 2-quinoxaloyl chloride in step i gave the title compound as a brown oil (18 mg).
M^-(ESI): 642.4
HPLC (Condition A), Rt: 5.74 min (HPLC purity: 88.1 %).

Example 147: [({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)(4-{[(4-phenoxybenzyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using 4-phenoxybenzylamine in step f and 4-methoxybenzenesulfonyl chloride in step i gave the title compound as a brown foam (33 mg).
M^-(LC/MS(ESI)): 670.8; M^+(LC/MS(ESI)): 672.0
HPLC (Condition A), Rt: 4.67 min (HPLC purity: 92.6 %).

Example 148: [{[1-(3-iodobenzoyl)-4-piperidinyl]methyl}(4-{[(4-phenoxybenzyl)-amino]carbonyl}benzyl)amino](oxo)acetic acid

The same procedure as employed in the preparation of Example 141 using 4-phenoxybenzyl-amine in step f and 3-iodobenzoyl chloride in step i gave the title compound as a brown oil (35 mg).
M^-(LC/MS(ESI)): 730.7; M^+(LC/MS(ESI)): 732.4
HPLC (Condition A), Rt: 4.68 min (HPLC purity: 90.9 %).

Example 149: oxo{(4-{[(4-phenoxybenzyl)amino]carbonyl}benzyl)[(1-{(2E)-3-[3-(trifluoromethyl)phenyl]-2-propenoyl}-4-piperidinyl)methyl]amino}acetic acid

The same procedure as employed in the preparation of Example 141 using phenoxybenzylamine in step f and trans-3-(trifluoromethyl)cinnamoyl chloride in step i gave the title compound as a brown foam (33 mg).
M^-(LC/MS(ESI)): 698; M^+(LC/MS(ESI)): 700
HPLC (Condition A), Rt: 4.95 min (HPLC purity: 89.3 %).

Example 150: Preparation of a pharmaceutical formulation

Pharmaceutical formulations using the compounds of formula (I) may be prepared according to standard procedures known to a person skilled in the art.

The following formulation examples illustrate representative pharmaceutical compositions using compounds of formula (I), while it is emphasised that the present invention is not to be construed as being limited to said the below formulations.

Formulation 1 – Tablets

An substituted methylene amide derivative of formula (I) is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active substituted methylene amide derivative per tablet) in a tablet press.

Formulation 2 – Capsules

Substituted methylene amide derivative of formula (I) is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of substituted methylene amide derivative per capsule).

Formulation 3 – Liquid

Substituted methylene amide derivative derivative of formula (I) (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added.

Formulation 4 – Tablets

A substituted methylene amide derivative of formula (I), is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 300-600 mg tablets (150-300 mg of active substituted methylene amide derivative) in a tablet press.

Formulation 5 – Injection

A substituted methylene amide derivative of formula (I), is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Example 151 : Biological assays

The compounds of formula (I), may be subjected to the following assays :

(1) The PTP Enzyme Assay

(2) The in vivo assay in db/db mice

(1) **The PTP Enzyme Assay (in vitro assay)**

The PTP Enzyme Assay aims at determining the extent of inhibition of PTP1B, SHP-1, SHP-2 or GLEPP-1 in the presence of a test compound. The inhibition is illustrated by IC_{50} values which denote the concentration necessary to achieve an inhibition of 50% of said PTP's using the following concentration of the substrate DiFMUP :

- 5 µM DiFMUP for PTP1b;
- 20 µM DiFMUP for SHP-1 and SHP-2;
- 30 µM DiFMUP for GLEPP-1.

a) PTPs cloning

The cloning and expression of the catalytic domain of PTP1B, may be performed as described in *J. Biol. Chem. 2000*, 275(13), pp 9792-9796.

b) Materials and Methods

The DiFMUP assay allows to follow the dephosphorylation of DiFMUP (6,8-DiFluoro-4-MethylUmbelliferyl Phosphate) - which is the PTP substrate – mediated by PTP into its stable hyrolysis product, i.e. DiFMU (6,8-difluoro-7-hydroxy coumarin). Due to its rather low pKa and its high quantum yield, DiFMU allows to measure both acidic and alkaline phosphatase activities with a great sensitivity.

Assays were performed in a 96 well plate format, using the catalytic core of a human recombinant PTP as the enzyme and 6,8-DiFluoro-4-MethylUmbelliferyl Phosphate (DiFMUP, Molecular Probes, D-6567) as a substrate. Compounds to be tested were dissolved in 100% DMSO at a concentration of 2 mM. Subsequent dilutions of the test compounds (to yield a concentration of 100, 30, 10, 3, 1,0.3, 0.1, 0.03, 0.01, 0.001 µM) were performed in 100 % DMSO using a Tecan Stand Alone Workstation. 5 µl of diluted compound or vehicle (100% DMSO = control) was distributed to a black Costar 96 well plate. 25µl of DiFMUP diluted in the assay buffer (20mM Tris HCl pH 7.5, 0.01% IGEPAL CA-630, 0.1mM ethylenediaminetetracetic acid, 1mM DL-Dithiothreitol) were added, followed by 20µl of human recombinant PTP enzyme diluted in assay buffer in order to start the enzymatic reaction. The reaction ran for 30 minutes at room temperature before reading the fluorescence intensity (integral or intensity) on a Perkin-Elmer Victor 2 spectrofluorimeter (excitation of 6,8-difluoro-7-hydroxy coumarin is at 355nm, the emission at 460 nm, for 0.1s). The percentage of inhibition is determined by measuring the relative fluorescence ion absence of a test compound (PTP inhibitor), i.e. with the solvent alone (5% DMSO). The IC_{50} values for inhibition were determined in triplicates.

The tested compounds according to formula (I) display an inhibition (illustrated by IC_{50} values) with regard to PTP of less than 10 µM, more preferred less than 5 µM.

For instance, the compound of example 10 displays an IC_{50} value of 2.224 µM in respect of PTP1B, an IC_{50} value of 1.40 in respect of GLEPP-1, an IC_{50} value of 2.40 and 2.70 in respect of SHP-1 and SHP-2.

The compound of example 4 displays an IC_{50} value of 0,916 µM in respect of PTP1B and an IC_{50} value of 0.50 in respect of GLEPP-1, an IC_{50} value of 1 and 1.4 in respect of SHP-1 and SHP-2.

(2) **In vivo assay in db/db mice**

The following assay aims at determining the anti-diabetic effect of the test compounds of formula (I), *in vivo* in db/db mice using fasted animals. The assay intends to determine the postprandial glycemia right after a predetermined diet.

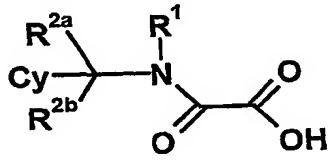
The assay was performed as follows :

Db/db mice were fasted during 20 hours. After oral administration, using CarboxyMethylCellulose (0.5%), Tween 20 (0.25%) and water as vehicle, of compounds of formula (I), they had access to commercial food (*ad libitum*). Blood glucose (postprandial glycemia) was determined before and 4 hrs after drug administration.

Treatment (p.o) of the animals with substituted methylene amide compounds of formula (I), at a dosage of 50 mg/kg, decreased the blood glucose level induced by food intake by about 20-40%. For instance, the compound of example 10 decreased the blood glucose level induced by food intake by about 27% at a dosage of 50 mg/kg.

Claims

1. Substituted methylene amide derivative of Formula (I) :



(I)

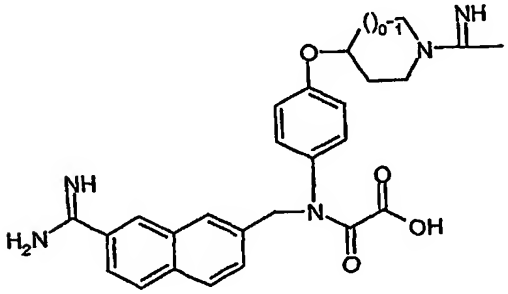
as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein

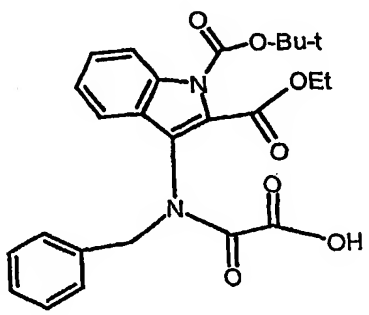
R^1 is selected from the group consisting of (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, (3-8-membered)-cycloalkyl or heterocycloalkyl, (C_1-C_{12})alkyl-aryl or (C_1-C_{12})alkyl-heteroaryl, (C_2-C_{12})alkenyl-aryl or -heteroaryl, (C_2-C_{12})alkynyl-aryl or -heteroaryl;

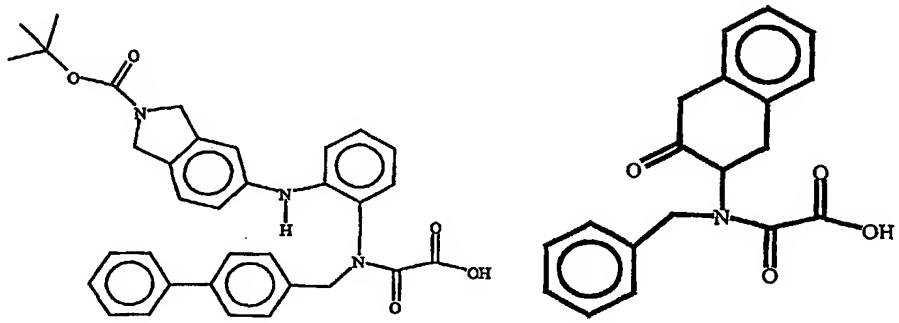
R^{2a} and R^{2b} are each independently from each other selected from the group comprising or consisting of H or (C_1-C_{12})alkyl;

Cy is an aryl, heteroaryl, cycloalkyl or heterocycle group,

with the proviso that the following compounds are excluded :







2. Substituted methylene amide derivatives according to claim 1, wherein R^{2a} and R^{2b} are each H.

3. A substituted methylene amide derivative according to claim 1 or 2, wherein Cy is a thienyl or a phenyl group.

4. A substituted methylene amide derivative according to claim 3, wherein Cy is a thienyl, phenyl being substituted by a phenyl or an oxadiazole group or by 1 or 2 moieties selected from the group consisting of -NH-CO-R^3, -SO_2-$NR^3R^{3'}$, or –CO-$NR^3R^{3'}$ in which R^3, $R^{3'}$ are independently selected from H, (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl, (C_1-C_{12})alkyl aryl or heteroaryl, (C_2-C_{12})alkenyl-aryl or -heteroaryl, (C_2-C_{12})alkynyl-aryl or -heteroaryl.

5. A substituted methylene amide derivative according to claim 4, wherein $R^{3'}$ is H and R^3 is selected from the group consisting of diphenyl-ethyl, dodecyl, octyl, 4-pentyl-benzyl, 4-phenoxy-phenethyl, ethyl-thiophen-2-yl, pentadecyl, tridecyl, hexyloxy-phenyl or (2-ethyl)-hexyl.

6. A substituted methylene amide derivative according to any of the preceding claims, wherein R^1 is a moiety $-CH_2$-A, or $-CH_2-CH_2$-A with A being an aryl, heteroaryl, 3-8-membered heterocycloalkyl or 3-8-membered cycloalkyl.

7. A substituted methylene amide derivative according to any of the preceding claims, wherein R^1 is A, with A being aryl, heteroaryl, 3-8-membered heterocycloalkyl or 3-8-membered cycloalkyl.

8. A substituted methylene amide derivative according to claim 6 or 7, wherein A is selected from the group consisting of phenyl, pyridinyl, benzo-1,3-dioxolenyl, biphenyl, naphtyl, quinoxalinyl, thiazolyl, thienyl, furanyl or a piperidinyl group, being optionally substituted by 1 or 2 cyano, halogen, NO_2, (C_1-C_6)alkoxy, aryloxy or heteroaryloxy, (C_1-C_6)thioalkoxy, (C_1-C_{12})alkyl, (C_1-C_{12})alkyl-X wherein X is halogen, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl, (C_1-C_{12})alkyl aryl or heteroaryl, (C_2-C_{12})alkenyl aryl or heteroaryl, (C_2-C_{12})alkynyl aryl or heteroaryl, $-COR^3$, $-COOR^3$, $-CO-NR^3R^{3'}$, $-NHCOR^3$, $-COR^3$, $-CO-Y-R^3$ wherein R^3 is a (C_1-C_{12})alkyl or (C_1-C_{12})alkenyl, $-SOR^3$, $-SO_2R^3$, $-SO_2NR^3R^{3'}$ with R^3, $R^{3'}$ being independently from each other selected from the group consisting of H, straight or branched (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, (3-8-membered)-cycloalkyl or heterocycloalkyl.

9. A substituted methylene amide derivative according to any of the preceding claims wherein:

R^{2a} and R^{2b} are each H;

R^1 is $-CH_2$-A, with A being phenyl or thienyl, optionally substituted by cyano, halogen, methoxy, hydroxy, phenoxy, $-NO_2$, trifluoromethyl;

Cy is a thienyl, phenyl or biphenyl being substituted by $-SO_2R^3$, $-CO-NR^3R^{3'}$ in which $R^{3'}$ is H and R^3 is (C_6-C_{12})alkyl.

10. A substituted methylene amide derivative according to any of the preceding claims selected from the following group:

(benzyl{4-[(dodecylamino)carbonyl] benzyl}amino)(oxo)acetic acid

oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}acetic acid

(benzyl{4-[(pentadecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

(benzyl{4-[(tridecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[benzyl(4-{[dodecyl(methyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

{(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]amino}-(oxo)acetic acid

([1-(tert-butoxycarbonyl)-4-piperidinyl]{4-[(dodecylamino)carbonyl]benzyl}-amino)-(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

({[1-(tert-butoxycarbonyl)-4-piperidinyl]methyl}{4-[(dodecylamino)carbonyl]-benzyl}amino)(oxo)acetic acid

oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetic acid

[benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetic acid

oxo{[4-(trifluoromethyl)benzyl][4-(10-undecenoylamino)benzyl]amino}acetic acid

oxo{{4-[(9E)-9-tetradecenoylamino]benzyl}[4-(trifluoromethyl)benzyl]amino}acetic acid

{benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetic acid

{{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)-acetic acid

oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]-amino}-acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(trifluoromethyl)benzyl]amino}-(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-carboxy-1-phenylethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-methoxy-1-methylethyl)amino](oxo)acetic acid

(4-bromo{4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

([2-(3-chlorophenyl)ethyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[2-(3-methoxyphenyl)ethyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[(d,l)-trans-2-phenylcyclopropyl]amino}-(oxo)acetic acid

([(d,l)-trans-2-(benzyloxy)cyclopentyl]{4-[(dodecylamino)carbonyl]benzyl}-amino)-(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}-4-phenoxyanilino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(1,2,3,4-tetrahydro-1-naphthalenyl)amino]-(oxo)acetic acid

((1-benzyl-4-piperidinyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[2-(4-phenoxyphenyl)ethyl]amino}(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[2-(2-phenoxyphenyl)ethyl]amino}(oxo)acetic acid

((2-[1,1'-biphenyl]-4-ylethyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

(([1,1'-biphenyl]-3-ylmethyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

(3-(benzyloxy){4-[(dodecylamino)carbonyl]benzyl}anilino)(oxo)acetic acid

([4-(benzoylamino)benzyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

N-(carboxycarbonyl)-N-{4-[(dodecylamino)carbonyl]benzyl}-3-phenyl-beta-alanine

{{4-[(dodecylamino)carbonyl]benzyl}[4-(1,2,3-thiadiazol-4-yl)benzyl]amino}-(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-pentylbenzyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(1-phenylethyl)amino](oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino}(oxo)acetic acid

(benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{3-[(dodecylamino)carbonyl]benzyl}[4-(methylsulfonyl)benzyl]amino}(oxo)acetic acid

((3-cyanobenzyl){3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{{3-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

[(4-chlorobenzyl)(3-{[(4-pentylbenzyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

oxo{[4-({[2-(2-thienyl)ethyl]amino}carbonyl)benzyl][4-(trifluoromethyl)-benzyl]amino}acetic acid

{benzyl[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]-amino}(oxo)acetic acid

{(3-cyanobenzyl)[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

{(4-chlorobenzyl)[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

{[(3'-{[(2,2-diphenylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

((3-cyanobenzyl){[3'-({[2-(4-phenoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}amino)(oxo)acetic acid

oxo{{[3'-({[2-(4-phenoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}-[4-(trifluoromethyl)benzyl]amino}acetic acid

[(3-cyanobenzyl)({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)amino]-(oxo)acetic acid

[(4-chlorobenzyl)({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)amino]-(oxo)acetic acid

{({3'-[(octylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)[4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

{(3-cyanobenzyl)[(3'-{[(3-phenylpropyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}(oxo)acetic acid

[(3-cyanobenzyl)({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino]-(oxo)acetic acid

[(4-chlorobenzyl)({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)-amino]-(oxo)acetic acid

{({3'-[(dodecylamino)carbonyl][1,1'-biphenyl]-4-yl}methyl)[4-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

{benzyl[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl]amino}-(oxo)acetic acid

{(3-cyanobenzyl)[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)-methyl]amino}(oxo)acetic acid

{(4-chlorobenzyl)[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)-methyl]amino}(oxo)acetic acid

oxo{[(3'-{[(4-pentylbenzyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoro-methyl)benzyl]amino}acetic acid

oxo{[(3'-{[(4-phenylbutyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoro-methyl)benzyl]amino}acetic acid

{(3-cyanobenzyl)[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)-methyl]amino}(oxo)acetic acid

{(4-chlorobenzyl)[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)-methyl]amino}(oxo)acetic acid

{[(3'-{[(2-mesitylethyl)amino]carbonyl}[1,1'-biphenyl]-4-yl)methyl][4-(trifluoro-methyl)benzyl]amino}(oxo)acetic acid

((4-chlorobenzyl){[3'-({[2-(4-methoxyphenyl)ethyl]amino}carbonyl)[1,1'-biphenyl]-4-yl]methyl}amino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-methoxybenzyl)amino](oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[4-(methylsulfonyl)benzyl]amino}(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-methoxybenzyl)amino](oxo)acetic acid

{{3-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[6-(trifluoromethyl)-3-pyridinyl]methyl}-amino)(oxo)acetic acid

4-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

({3-[(dodecylamino)carbonyl]benzyl}{4-[hydroxy(oxido)amino]benzyl}-amino)(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(2-fluorobenzyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(2-pyridinylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(3-thienylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-hydroxybenzyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-phenoxybenzyl)amino](oxo)acetic acid

({3-[(dodecylamino)carbonyl]benzyl}{[6-(trifluoromethyl)-3-pyridinyl]methyl}-amino)(oxo)acetic acid

3-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

5-[((carboxycarbonyl){3-[(dodecylamino)carbonyl]benzyl}amino)methyl]-2-thiophenecarboxylic acid

({4-[(dodecylamino)carbonyl]benzyl}{4-[hydroxy(oxido)amino]-benzyl}-amino)-(oxo)acetic acid

((1,3-benzodioxol-5-ylmethyl){4-[(dodecylamino)carbonyl]-benzyl}amino)-(oxo)-acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-fluorobenzyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-phenoxybenzyl)amino](oxo)acetic acid

4-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

5-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]-2-thiophenecarboxylic acid

[{3-[(dodecylamino)carbonyl]benzyl}(2-thienylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(isopropyl)amino](oxo)acetic acid

((3,5-dichlorobenzyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[(3,5-dichlorobenzyl)(4-{[(3,3-diphenylpropyl)amino]carbonyl}-benzyl)amino]-(oxo)acetic acid

[(4-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]carbonyl}benzyl)(3,5-dichlorobenzyl)-amino](oxo)acetic acid

[(1,3-benzodioxol-5-ylmethyl)(4-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]carbonyl}-benzyl)amino](oxo)acetic acid

(2,3-dihydro-1H-inden-1-yl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

{2,3-dihydro-1H-inden-1-yl[4-({[2-(4-phenoxyphenyl)ethyl]amino}-carbonyl)-benzyl]amino}(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-pyridinylmethyl)amino](oxo)acetic acid

([4-(dimethylamino)benzyl]{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(3-pyridinylmethyl)amino](oxo)acetic acid

((4-cyanobenzyl){4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(1,3-thiazol-2-ylmethyl)amino](oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-amino)(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(4-pyridinylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(3-pyridinylmethyl)amino](oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(3-hydroxybenzyl)amino](oxo)acetic acid

((4-cyanobenzyl){3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetic acid

[{3-[(dodecylamino)carbonyl]benzyl}(1,3-thiazol-2-ylmethyl)amino](oxo)acetic acid

({3-[(dodecylamino)carbonyl]benzyl}{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-amino)(oxo)acetic acid

((1,3-benzodioxol-5-ylmethyl){3-[(dodecylamino)carbonyl]-benzyl}amino)-(oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-thienylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(2-pyridinylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(3-thienylmethyl)amino](oxo)acetic acid

[{4-[(dodecylamino)carbonyl]benzyl}(4-hydroxybenzyl)amino](oxo)acetic acid

3-[((carboxycarbonyl){4-[(dodecylamino)carbonyl]benzyl}amino)methyl]benzoic acid

[cyclopentyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

[benzyl({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

(({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl){3-[hydroxy(oxido)amino]-benzyl}-amino)(oxo)acetic acid

[({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(4-methoxybenzyl)amino]-(oxo)-acetic acid

[({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(2-fluorobenzyl)amino](oxo)acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[4-(methylsulfonyl)-benzyl]-amino}(oxo)acetic acid

[({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)(4-phenoxybenzyl)amino]-(oxo)-acetic acid

4-{[(carboxycarbonyl)({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)-amino]-methyl}benzoic acid

(({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl){[6-(trifluoromethyl)-3-pyridinyl]-methyl}amino)(oxo)acetic acid

{({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)[3-(trifluoromethyl)benzyl]amino}-(oxo)acetic acid

[(3-chlorobenzyl)({5-[(dodecylamino)sulfonyl]-2-thienyl}methyl)amino](oxo)acetic acid

{[(5-{[(3,3-diphenylpropyl)amino]sulfonyl}-2-thienyl)methyl][3-(trifluoromethyl)-benzyl]amino}(oxo)acetic acid

{(3-chlorobenzyl)[(5-{[(3,3-diphenylpropyl)amino]sulfonyl}-2-thienyl)methyl]-amino}(oxo)acetic acid

oxo{{[5-({[2-(4-phenoxyphenyl)ethyl]amino}sulfonyl)-2-thienyl]methyl}[3-(trifluoromethyl)benzyl]amino}acetic acid

((3-chlorobenzyl){[5-({[2-(4-phenoxyphenyl)ethyl]amino}sulfonyl)-2-thienyl]-methyl}amino)(oxo)acetic acid

{[(5-{[(2-[1,1'-biphenyl]-4-ylethyl)amino]sulfonyl}-2-thienyl)methyl][3-(trifluoro-methyl)benzyl]amino}(oxo)acetic acid

(({1-[(cyclohexylamino)carbonyl]-4-piperidinyl}methyl){4-[(dodecylamino)-carbonyl]benzyl}amino)(oxo)acetic acid

([(1-{[4-(dimethylamino)anilino]carbonyl}-4-piperidinyl)methyl]{4-[(dodecyl-amino)carbonyl]benzyl}amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[(1-hexanoyl-4-piperidinyl)methyl]-amino}-(oxo)acetic acid

({4-[(dodecylamino)carbonyl]benzyl}{[1-(3-iodobenzoyl)-4-piperidinyl]methyl}-amino)(oxo)acetic acid

{{4-[(dodecylamino)carbonyl]benzyl}[(1-{(2E)-3-[3-(trifluoromethyl)phenyl]-2-propenoyl}-4-piperidinyl)methyl]amino}(oxo)acetic acid

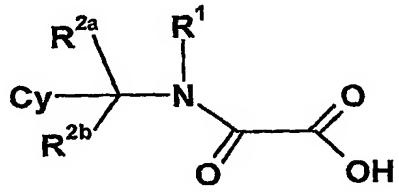
({4-[(dodecylamino)carbonyl]benzyl}{[1-(2-quinoxalinylcarbonyl)-4-piperidinyl]-methyl}amino)(oxo)acetic acid

[({1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}methyl)(4-{[(4-phenoxybenzyl)amino]carbonyl}benzyl)amino](oxo)acetic acid

[{[1-(3-iodobenzoyl)-4-piperidinyl]methyl}(4-{[(4-phenoxybenzyl)amino]-carbonyl}benzyl)amino](oxo)acetic acid

oxo{(4-{[(4-phenoxybenzyl)amino]carbonyl}benzyl)[(1-{(2E)-3-[3-(trifluoromethyl)phenyl]-2-propenoyl}-4-piperidinyl)methyl]amino}acetic acid

11. Substituted methylene amide derivative of Formula (I) :



(I)

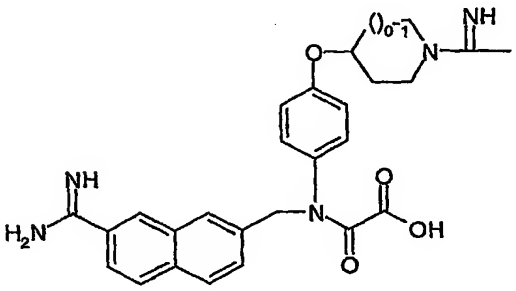
as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein

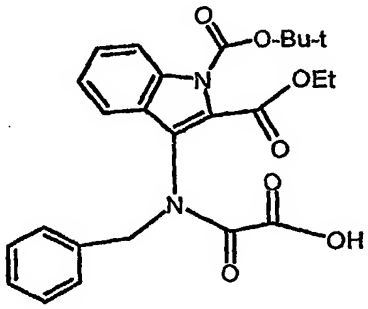
R^1 is selected from the group consisting of $(C_1\text{-}C_{12})$alkyl, $(C_2\text{-}C_{12})$alkenyl, $(C_2\text{-}C_{12})$alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl, $(C_1\text{-}C_{12})$alkyl-aryl or $(C_1\text{-}C_{12})$alkyl-heteroaryl, $(C_2\text{-}C_{12})$alkenyl-aryl or -heteroaryl, $(C_2\text{-}C_{12})$alkynyl-aryl or -heteroaryl;

R^{2a} and R^{2b} are each independently from each other selected from the group comprising or consisting of H or $(C_1\text{-}C_{12})$alkyl;

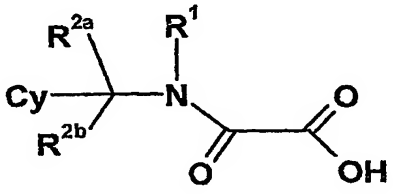
Cy is an aryl, heteroaryl, cycloalkyl or heterocycle, for use as a medicament,

with the proviso that the following compounds are excluded :





12. Use of a substituted methylene amide derivative according to formula (I):



(I)

as well as its geometrical isomers, its optically active forms as enantiomers, diastereomers and its racemate forms, as well as pharmaceutically acceptable salts and pharmaceutically active derivatives thereof, wherein

R^1 is selected from the group consisting of H, (C_1-C_{12})alkyl, (C_2-C_{12})alkenyl, (C_2-C_{12})alkynyl, aryl, heteroaryl, 3-8-membered cycloalkyl or heterocycloalkyl, (C_1-C_{12})alkyl-aryl or (C_1-C_{12})alkyl-heteroaryl, (C_2-C_{12})alkenyl-aryl or -heteroaryl, (C_2-C_{12})alkynyl-aryl or -heteroaryl;

R^{2a} and R^{2b} are each independently from each other selected from the group comprising or consisting of H or (C_1-C_{12})alkyl;

Cy is an aryl, heteroaryl, cycloalkyl or heterocycle, for the preparation of a pharmaceutical composition for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS).

13. Use of a substituted methylene amide derivative according to claim 12 for the preparation of a pharmaceutical composition for the modulation of the activity of PTPs.

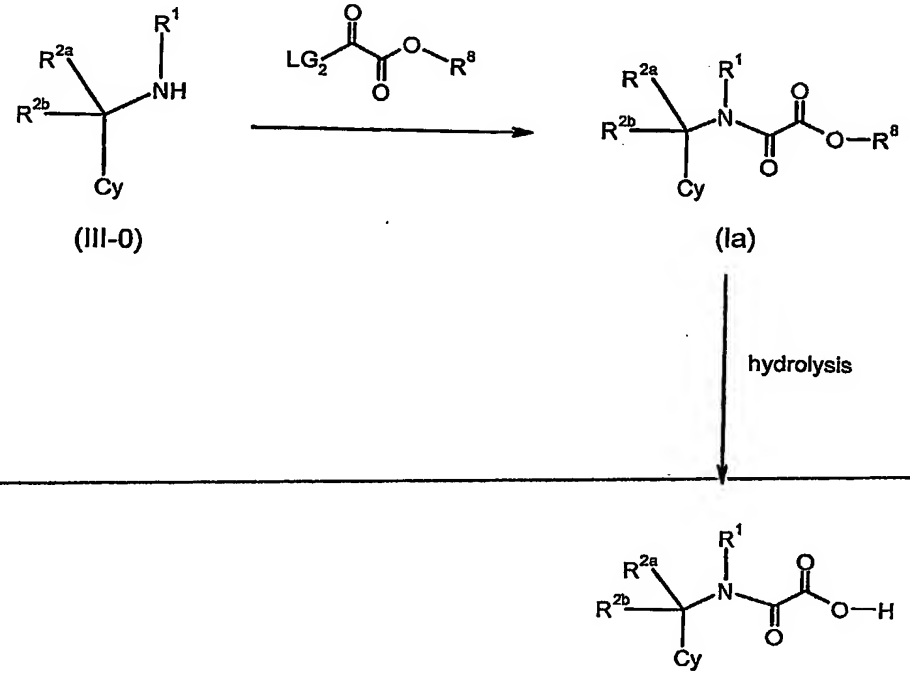
14. Use according to claim 13 wherein the PTP is PTP1B.

15. Use according to claim 14 wherein said modulation consists in the inhibition of PTP1B.

16. Use according to claim 15 for the treatment or prevention of disorders mediated by PTP1B.

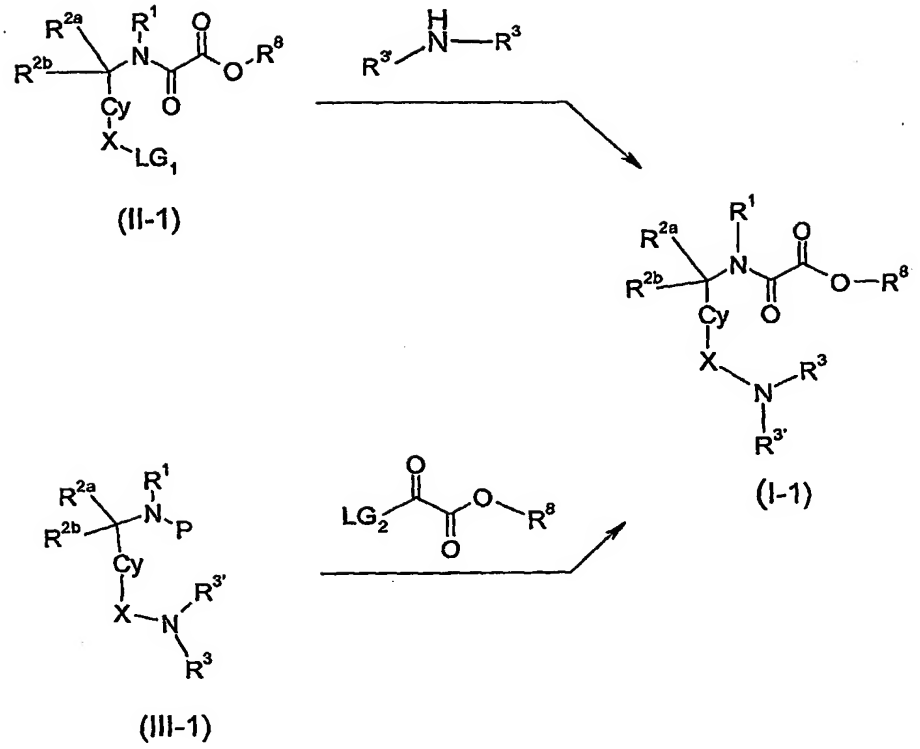
17. A pharmaceutical composition containing at least one substituted methylene amide derivative according to any of claims 1 to 10 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

18. A method of preparing a substituted methylene amide derivative of formula (I) according to any of claims 1 to 10, comprising the coupling step between amine derivative of formula (III-0) and an ester of formula LG_2-CO-CO-OR^8, followed by a hydrolysis:



wherein Cy, R^1, R^{2a}, R^{2b} are as above-defined, R^8 is a C_1-C_6 alkyl or cycloalkyl and LG_2 is a leaving group selected from Cl, N-hydroxy succinimide or benzotriazol-1-yl.

19. A method of prepation of a substituted methylene amide derivative of formula (I) according to claim 18, comprising the step of providing the corresponding ester of formula (I-1):



(II-1)

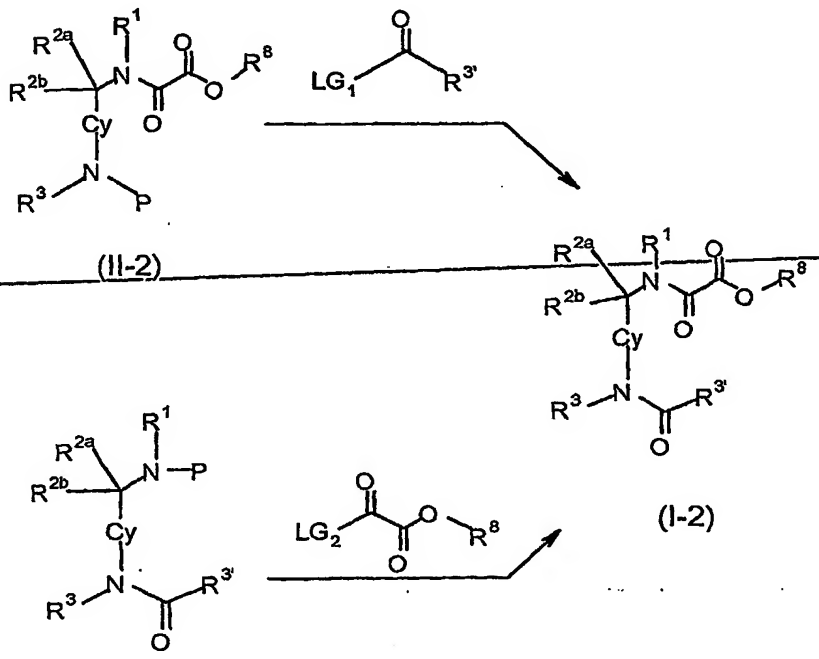
(I-1)

(III-1)

wherein X is -CO- or -SO_2-, LG_1 is Cl, OH, -OBn, O-Alkyl or O-Alkylaryl and LG_2 is selected from Cl, N-hydroxy succinimide or benzotriazol-1-yl, R^8 is a C_1-C_6 alkyl or cycloalkyl, P is a protective group selected from Boc or Fmoc, R^1, R^{2a}, R^{2b}, R^3 and $R^{3'}$ are as above defined;

and a subsequent hydrolysis step thus yielding the methylene amide derivative of formula (I).

20. A method of preparing a substituted methylene amide derivative of formula (I) according to claim 18, comprising of the step of providing the corresponding ester of formula (I-2):



(II-2) (I-2)

(III-2)

wherein LG_1 is Cl, OH, OBn, O-Alkyl or O-Alkylaryl and LG_2 is selected from Cl, N-hydroxy succinimide or benzotriazol-1-yl, R^8 is a C_1-C_6 alkyl or cycloalkyl, P is a protective group selected from Boc or Fmoc, R^1, R^{2a}, R^{2b}, R^3 and $R^{3'}$ are as above defined;

and a subsequent hydrolysis step, thus yielding the methylene amide derivative of formula (I).

21. A substituted methylene amide derivative of any of Formulae (I-1) or (I-2) which is selected from the group consisting of:

benzyl 4-({benzyl[ethoxy(oxo)acetyl]amino}methyl)benzoate

ethyl (benzyl{4-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate

benzyl 4-({[ethoxy(oxo)acetyl][4-(trifluoromethyl)benzyl]amino}methyl)benzoate

ethyl oxo{{4-[(pentadecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]-amino}acetate

ethyl {(4-{[dodecyl(methyl)amino]carbonyl}benzyl)[4-(trifluoromethyl)benzyl]-amino}(oxo)acetate

tert-butyl 4-{{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}-piperidine-1-carboxylate

tert-butyl 4-{{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}-piperidine-1-carboxylate

ethyl {{4-[(dodecylamino)carbonyl]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)acetate

ethyl {{4-[(dodecylamino)carbonyl]benzyl}[3-(trifluoromethyl)benzyl]amino}-(oxo)acetate

tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)-acetyl]amino}-methyl)-piperidine-1-carboxylate

ethyl {{4-[(tert-butoxycarbonyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)acetate

ethyl {(4-aminobenzyl)[4-(trifluoromethyl)benzyl]amino}(oxo)acetate

ethyl oxo{[4-(tridecanoylamino)benzyl][4-(trifluoromethyl)benzyl]amino}acetate

ethyl [benzyl(4-{[4-(hexyloxy)benzoyl]amino}benzyl)amino](oxo)acetate

ethyl (benzyl{4-[(tert-butoxycarbonyl)amino]benzyl}amino)(oxo)acetate

ethyl [(4-aminobenzyl)(benzyl)amino](oxo)acetate

ethyl oxo{[4-(trifluoromethyl)benzyl][4-(undec-10-enoylamino)benzyl]-amino}acetate

ethyl oxo{{4-[(9E)-tetradec-9-enoylamino]benzyl}[4-(trifluoromethyl)benzyl]-amino}-acetate

ethyl {benzyl[4-(tridecanoylamino)benzyl]amino}(oxo)acetate

ethyl {{4-[(2-hydroxydodecyl)amino]benzyl}[4-(trifluoromethyl)benzyl]amino}-(oxo)acetate

ethyl oxo{[4-(trifluoromethyl)benzyl][4-(3-undecyl-1,2,4-oxadiazol-5-yl)benzyl]-amino}acetate

ethyl {({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)[4-(trifluoromethyl)benzyl]-amino}(oxo)acetate

tert-butyl 4-({{4-[(benzyloxy)carbonyl]benzyl}[ethoxy(oxo)acetyl]amino}-methyl)-piperidine-1-carboxylate

ethyl [{4-[(dodecylamino)carbonyl]benzyl}({1-[(4-methoxyphenyl)sulfonyl]-piperidin-4-yl}methyl)amino](oxo)acetate

ethyl {{4-[(dodecylamino)carbonyl]benzyl}[1-(1-naphthyl)ethyl]amino}(oxo)-acetate

ethyl (benzyl{3-[(dodecylamino)carbonyl]benzyl}amino)(oxo)acetate

ethyl [benzyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino](oxo)acetate

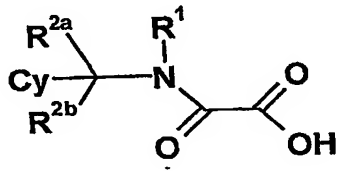
tert-butyl 4-({{4-[(dodecylamino)carbonyl]benzyl}[ethoxy(oxo)acetyl]-amino}-methyl)-piperidine-1-carboxylate

ethyl [{4-[(dodecylamino)carbonyl]benzyl}(piperidin-4-ylmethyl)amino](oxo)-acetate

ethyl [cyclopentyl({5-[(dodecylamino)sulfonyl]thien-2-yl}methyl)amino]-(oxo)acetate.

Abstract of the invention:

The present invention is related to substituted methylene amide derivatives of formula (I) and use thereof for the treatment and/or prevention of metabolic disorders mediated by insulin resistance or hyperglycemia, comprising diabetes type I and/or II, inadequate glucose tolerance, insulin resistance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, obesity, polycystic ovary syndrome (PCOS). In particular, the present invention is related to the use of substituted methylene amide derivatives of formula (I) to modulate, notably to inhibit the activity of PTPs. The present invention is furthermore related to novel substituted methylene amide derivatives and method of preparation thereof.



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